Theory and Research in Health Sciences II

Volume 2

EDITOR

Prof. Dr. Cem Evereklioğlu[1]

1 Erciyes University Medical Faculty, Department of Ophthalmology, Kayseri, Turkey
E-mail: everekliogl u@erciyes.edu.tr

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Prof. Dr. Cem Evereklioğlu[1]

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İÇİNDEKİLER

Chapter 21

THE ROLE OF DISINFECTION

Duygu Öcal ŞEN[1],
Doç. Dr. Dilek ÖZTAŞ[2],
Prof. Dr. Ergun ERASLAN[3]

1 Ankara Yıldırım Beyazıt University, Institute of Science, Occupational Health and Safety Program (Ph.D. Student), duyguocalsen@gmail.com, Orcid No: 0000-0002-8604-8210
2 Doç. Dr., Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Internal Medical Sciences, doztas@ybu.edu.tr, Orcid No: 0000 0002 8687 7238
3 Prof. Dr, Ankara Yıldırım Beyazıt University, Faculty of Engineering and Natural Sciences, Department of Industrial Engineering, eraslan@ybu.edu.tr, Orcid No: 0000-0002-5667-0391

1. Introduction

Disinfection has been used to solve hygiene issues in many areas from past to present. The control of microorganisms is of great importance in areas such as industry, medicine, veterinary medicine, food, and the environment (McDonnel G, 2007). Hand tools, laboratory equipment, and other materials used in these sectors can be contaminated with organisms parallel to the nature of the operations handled in these sectors. Various disinfection and sterilization methods have been developed as the level of knowledge about microorganisms and the problems caused by the infection have increased (McDonnel G, 2007). Before the information on this subject became clear in the past, various disinfection methods were tried both to prevent epidemics and to heal wounds. Keeping microorganisms under control and preventing their growth and contamination is critical. In this context, disinfection processes are indispensable both in various sectors and in daily life.

Cleaning is defined as the elimination of the contamination and unwanted materials from an area for the planned use (McDonnel G, 2007). Those unwanted materials may be dirt, stain, rust, or infectious agents. According to the type and amount of the contaminant various kinds of cleaning take place. Disinfection is a process that wipes out most of the microorganisms but not the resistant bacterial spores on lifeless items (Rutala WA, Weber DJ; Healthcare Infection Control Practices Advisory Committee, 2008). Sterilization is a process that kills viable organisms on a surface inclusive of bacterial spores (McDonnel G, 2007). Disinfection removes most of the microbes but in order to receive a hygienic step, killing all the alive microorganisms is necessary for some sectors. Disinfectants are chemical agents that can inactivate or destroy vegetal microorganisms; moreover, all of them are biocides (Moldenhauer J, 2019).

Disinfectants used in daily life are key elements for cleaning. Disinfection is critical in order to prevent diseases; in this context, it becomes crucial during endemic or pandemic situations. The people in the world have encountered global health problems like the Ebola Virus in 2014, H1N1 in 2009, and the SARS Virus in 2003 (Chatterjee R et. al., 2020). Starting from the last days of 2019 a form of pneumonia was first to catch in Wuhan, the capital city of Hubei Province, China then it was reported to the World Health Organization (WHO) on 31st December 2019 (McAleer M, 2020). Afterward, WHO declared COVID-19 as a Public Health Emergency of International Concern (PHEIC) on the 30th of January 2020 (Kelland and Nebehay 2020). Finally, WHO gave this newly discovered coronavirus disease the name Covid-19 in February 2020 (McAleer M, 2020). The disinfection process is one of the most critical defense mechanisms that can be used individually within the scope of combating the Covid-19 pandemic, which the world is in as of 2020.

The History of Disinfection

It is known that the use of disinfection goes back in history. Given the historical development of disinfection, the oldest reference to the disinfection of buildings with a chemical product is described in 800 BC by Homer in book xii of the Odyssey, stated as the hero wanted that sulphur to be burnt in the house after a battle in his house (Block SS, 1991). The purifying effect of sulphur was occupied in many cases after a while. At that time the use of sulfur for disinfection was common and necessary. Susruta, in his book Susruta-tantra, required the sulphur to be burned in rooms where surgical operations were to take place in the 4th century AD, in India (Karasszon D, 1988). During the plague epidemics of the Middle Ages, sulphur was also suggested for disinfecting contaminated establishments and objects in Europe (Block SS, 1991). Therefore, it has been observed that sulphur compounds are used in various fields in disinfection in history. It was obvious that forms of sulphur are not the only chemical that was used as a disinfectant in ancient times. Mercurial compounds were used not only as disinfectants but also as a barrier paint or coating in Egypt, China, India, and Europe in ancient times (Block SS, 1991). Mercury compounds have been used as a disinfectant in different countries of the world. In addition, strong acids and organic acids have been used as disinfectants in history. Their use has become widespread because they are powerful and effective. The ancient Egyptians used palm wine and vinegar to wash the abdominal cavities of human and animal cadavers before mummifying them around 3000 BC (Karasszon D, 1988). Another disinfection method in history is fumigation. Fumigation is basically a method that kills the pests using gaseous fumigants. In order to control an epidemic that influenced both people and animals, Hippocrates suggested fumigation in 429 BC (Karasszon D, 1988). As it can be seen from the variety of examples, disinfection has been a need in human life in different areas such as surgical cleaning, struggling with epidemic, or mummifying. Nowadays, since the world faces the pandemic problem once again, the importance of disinfection has come into prominence. One of the basic precautions that need to be taken into consideration is making sure the cleanness of the humans' hands and environment/surface cleaning. To achieve this, various types of disinfection have been required in different areas of life. By following various government publications, people understand which types of disinfection and which kind of disinfectant they can use to protect themselves both at their homes and workplaces.

2. Types of Disinfection

Disinfection is divided into two as physical and chemical disinfection in principle (Figure 1). The most commonly used methods of physical disinfection are heat, cold, filtration, and radiation (McDonnel G, 2007).

Physical disinfection types are selected according to usage needs. Some processes require heat and some need radiation. In chemical disinfection, chemical biocides are used according to their ability to kill microorganisms. These biocides are classified as acids and acid derivatives, alkalis or bases, alcohols, antimicrobial metals, aldehydes, anilides, antimicrobial dyes, biguanides, diamidines, essential oils and plant extracts, halogens and halogen-releasing agents, metals, peroxygens and other forms of oxygen, phenolics, antiseptic phenolics, quaternary ammonium compounds and surfactants, halogens and other miscellaneous biocides or applications. (McDonnel G, 2007). As defined in the physical disinfection, the operation needs define which agent to use in related disinfection process. There are many of different kind of disinfectants that are used in chemical disinfection on the market. It is necessary to choose the ones that the most applicable to the given occupation. Moreover, it is important to use the approved disinfectants in order to minimize the health risks may cause from them.

During the physical and chemical disinfection processes, all necessary precautions should be taken to protect the employees from the negative effects of the disinfection operation. In physical disinfection, from the negative effects of heat, coldness, radiation, and filtration processes, and from the negative effects of disinfectants in chemical disinfection, people should start from collective protection measures within the scope of the risk control hierarchy (CDC NIOSH, 2020) and take measures that end in personal protective equipment (Figure 2). In all types of disinfection, caring about human health should be the number one priority. In all operations, related hazards should be identified and measures should be taken. According to the hierarchy of control, the most effective countermeasure is physically removing the hazard by name elimination. If this is not possible then the next step will be followed as substitution which is replacing the hazard with a less hazardous substance or process. If this solution is not enough or not applicable the next step will be taking engineering controls to isolate people from hazards. The remaining two steps will be taken after the trial of the first three steps. The next one is taking administrative controls in order to change the way people work such as making different shift arrangements or changing the number of employees that work in a related area. Finally, the last and least effective countermeasure is protecting the worker with personal protective equipment. In some operations completing that operation without personal protective equipment is not possible. Even under that circumstance, all the other steps of the risk control hierarchy model should be reviewed before considering a personal protective equipment solution.

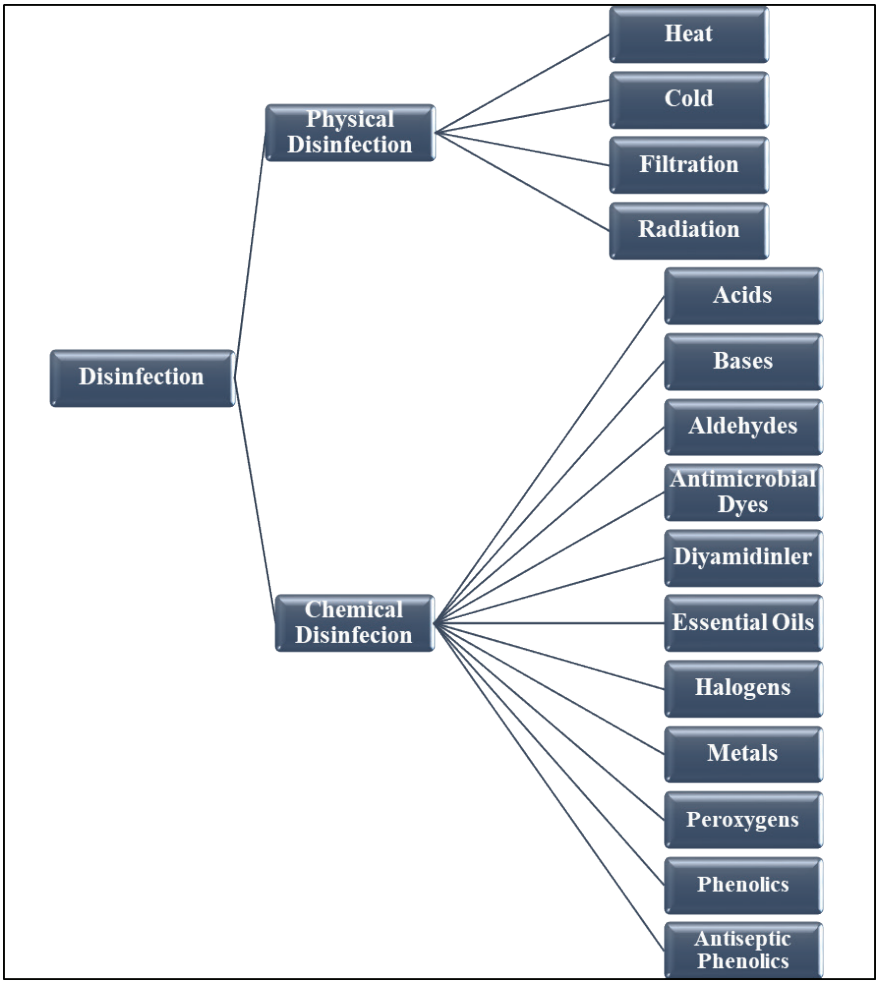

Figure 1 Types of Disinfection

3. **Properties of an Ideal Disinfectant**

Having an ideal, good property disinfectant is crucial in terms of saving energy and money. If the disinfectant's properties are poor, the cleaning process will be unsuccessful; moreover, additional work needed to be performed in order to achieve the desired outcome. This may result in a waste of water, time, energy, money, and the workforce. Therefore, choosing the right disinfectant for the intended cleaning operation is necessary.

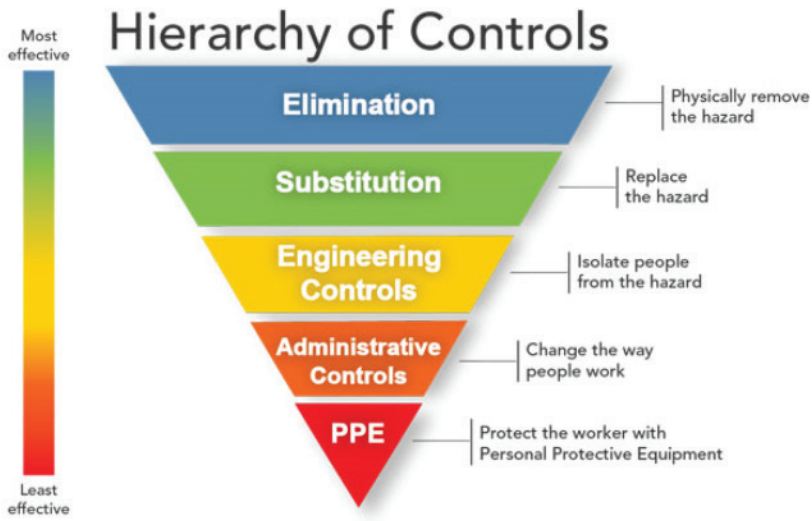

Figure 2 Hierarchy of Controls

The properties of an ideal disinfectant were described as follows (Rutala and Weber, 2008):

- Broad-spectrum
- Fast-acting
- Not affected by environmental factors
- Nontoxic
- Surface compatibility
- Residual effect on treated surfaces
- Easy to use with clear label directions
- Odorless
- Economical
- Solubility
- Stability
- Cleaner
- Environmentally friendly

Firstly, an ideal disinfectant should have a wide spectrum to affect as many microorganisms as possible and it needs to act fast so that it can rapidly kill them. Moreover, it should not be affected by environmental parameters and it should not be harmful to the people or the environment.

Moreover, in the disposal process it should also be environmental-friendly. The ideal disinfectant should have surface compatibility property. It should not be harmful to surfaces or substances. Besides, it should not leave any residual layer on surfaces. It needs to be used easily not to cause any energy or workforce losses and the warning and information labels should be clear. It should be odorless in order not to cause any allergy or disturbance. Furthermore, it needs to be soluble in water and stable. Being economical is another critical factor for the ideal disinfectant because in industrial usage tons of kilograms will be needed continuously. Last but not least, an ideal disinfectant should have nice cleaning properties.

4. Covid-19 and Disinfection

Starting from the last days of 2019 a form of pneumonia was first to catch in Wuhan, the capital city of Hubei Province, China then it was reported to the WHO (McAleer M, 2020). Approximately two months later WHO declared pneumonia as pandemic and named the responsible virus as Covid-19. Starting from the first day it appears, Covid-19 keeps affecting human lives continuously. The main way to protect people from Covid-19 is disinfection. In this concern, starting from WHO publications, a lot of countries created papers, posters, and valuable documents to spread people the logic. Cleaning with soap and water will decrease the virus amount on surfaces and objects (CDC, 2019). Moreover, disinfection with the United States Environmental Protection Agency (EPA) approved disinfectants against Covid-19 can also help to reduce the spread of virus risk (Table 1). If EPA approved disinfectants are not available, some other alternative disinfectants can be used carefully such as 1/3 cup of 5.25%–8.25% bleach added to 1 gallon of water, or 70% alcohol solutions (CDC,2019).

Table 1 Active ingredient-based EPA approved Covid-19 disinfectant example list

EPA Reg. Number	*Active Ingredient (s)*	*Product Name*	*Company*	*Virus*	*T min*	*Form. Type*	*Surface Type*	*Use Site*
10324-105	Quaternary ammonium	Maquat 128-PD	Mason Chemical Company	Human coronavirus	10	Dilutable	Hard Nonporous (HN)	Healthcare; Institutional; Residential
10324-230	Hydrogen peroxide; Peroxyacetic acid (Peracetic acid)	Maguard 1522	Mason Chemical Company	Human coronavirus	1	Dilutable	Hard Nonporous (HN)	Healthcare; Institutional; Residential
0492-5	Quaternary ammonium; Isopropanol (Isopropyl alcohol)	Discide Ultra Disinfecting Spray	Palmero Healthcare LLC	Human coronavirus	0.5	Ready-to-use	Hard Nonporous (HN)	Healthcare; Institutional; Residential
1677-241	Sodium hypochlorite	Hydris	Ecolab Inc	Human coronavirus	5	Ready-to-use	Hard Nonporous (HN)	Healthcare; Institutional
1677-204	Octanoic acid	65 Disinfecting Heavy Duty Acid Bathroom Cleaner	Ecolab Inc	Human coronavirus	2	Dilutable	Hard Nonporous (HN)	Healthcare; Institutional

4091-23	Sodium hypochlorite; Sodium carbonate	Mold Armor Formula 400	W.M. Barr & Company Inc	Human coronavirus	0.5	Ready-to-use	Hard Nonporous (HN)	Institutional; Residential
42964-17	Quaternary ammonium; Ethanol (Ethyl alcohol)	Asepticare	Airkem professional products	Human coronavirus	2	Ready-to-use	Hard Nonporous (HN)	Healthcare; Institutional; Residential
4822-606	L-Lactic acid	Fangio	S.C. Johnson & Son Inc	Human coronavirus	10	Ready-to-use	Hard Nonporous (HN)	Institutional; Residential
98-134	Ethanol (Ethyl alcohol); Phenolic	Spraypak Spray Disinfectant Formula 2	Chase Products Co	Human coronavirus	10	Ready-to-use	Hard Nonporous (HN)	Healthcare; Institutional
54289-4	Peroxyacetic acid (Peracetic acid)	Peraclean 15 (Peroxyacetic Acid Solution)	Evonik Corporation	Human coronavirus	1	Dilutable	Hard Nonporous (HN)	Healthcare; Institutional
5813-86	Glycolic acid	CBW	The Clorox Company	Human coronavirus	10	Impregnated materials	Hard Nonporous (HN)	Residential
0627-6	Phenolic	Phenolic Disinfectant HG	Diversey Inc	Human coronavirus	10	Dilutable	Hard Nonporous (HN); Food Contact Post-Rinse Required (FCR)	Healthcare; Institutional
74986-5	Sodium chlorite	Selectrocide 5g	Selective Micro Technologies LLC	Human coronavirus	10	Solid	Hard Nonporous (HN)	Healthcare; Institutional
777-136	Ethanol (Ethyl alcohol)	Lysol Neutra Air® 2 in 1	Reckitt Benckiser LLC	Human coronavirus	0.5	Ready-to-use	Hard Nonporous (HN); Food Contact Post-Rinse Required (FCR)	Healthcare; Institutional; Residential
777-139	Citric acid	T-bone	Reckitt Benckiser LLC	Human coronavirus	5	Wipe	Hard Nonporous (HN); Food Contact Post-Rinse Required (FCR)	Healthcare; Institutional; Residential
89896-2	Hypochlorous acid	Cleansmart	Simple Science Limited	Human coronavirus	10	Ready-to-use	Hard Nonporous (HN); Food Contact No Rinse (FCNR)	Healthcare; Institutional; Residential
91176-2	1,2-Hexanediol	PELS 422	The Gilla Company LLC	Human coronavirus	10	Ready-to-use	Hard Nonporous (HN)	Healthcare; Institutional
9402-17	Hydrogen peroxide; Ammonium carbonate; Ammonium bicarbonate	Hitman Wipe	Kimberly-Clark Global Sales LLC	Human coronavirus	6	Wipe	Hard Nonporous (HN)	Institutional; Residential

EPA also defines the steps for safe and effective disinfectant usage as follows (EPA, 2019):

1. Checking the product for EPA approval
2. Read the directions
3. Pre-clean the surface

4. Obey the contact time
5. Wear gloves and wash your hands
6. Lock it up

It is important to buy and use ministry or any public authority approved chemicals at homes and in industry. After getting the product following the directions about safe usage and precautionary statements. Identifying the hazards and control measures of the substance will protect people's health. Moreover, usage restrictions, hazard signs, the proper way to use directions are critical. If visible dirt is available on the surface that will be cleaned, before using the disinfectant, cleaning with soap and water is beneficial. For the disinfectant to be effective, the contact time that is defined in the directions should be followed. After that step, adequate disinfection can take place. As in all processes, the last step will be the usage of personal protective equipment. The glove usage is essential to protect the hands from the negative effects of both disinfectant and the dirt that needs to be cleaned. Both for Covid-19 disinfection and other kinds of disinfection, after the usage of gloves, hands should be washed after using the gloves. After the disinfection is over, disinfectants should be kept tightly closed and they should be removed to some place that children and also unauthorized people cannot reach.

5. Conclusion and Suggestion

Disinfection has been an important part of human lives for a long time. They use it in a variety of sectors such as medicine, food, and the environment (McDonnel G, 2007). Not only in the mentioned sectors but also different areas people have been making disinfection operations since ancient times. Struggling with pandemic periods the necessity of disinfection comes into consideration in world history. Nowadays, everybody is using different disinfection methods in order to cope with the Covid-19 Pandemic. To avoid virus transmission, the Centers for Disease Control and Prevention suggests hand washing with soap and water and surface disinfection with defined chemicals.

One of the most crucial things during the disinfection process even it is physical or chemical, following the safety rules. People should protect themselves and employers should protect their employees by detecting the risks and taking countermeasures with respect to the risk control hierarchy. In order to achieve this elimination, substitution, making engineering controls, applying administrative controls, and using personal protective equipment should be the order. If those steps are followed and people start the process after minimizing the risks, accidents related to chemical usage or physical agents during disinfection may be reduced.

Disinfectant is one of the basic components of disinfection. Choosing the ideal disinfectant is another key point in the disinfection process. To prevent time and money losses, choosing the correct disinfectant for related cleaning activity is necessary. The ideal disinfectant should be fast-acting, non-toxic, surface compatible, odorless, user friendly, economical, soluble, stable, clean, and environmentally friendly (Rutala and Weber, 2008). After choosing the right disinfection process, correct disinfectant, and following the instructions that are related to it, safe and efficient disinfection can take place.

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Chapter 22

ORAL CANCER

Dr. Öğr. Üyesi Muhammet Bahattin BİNGÜL[1]

1 Dr.Öğr.Üyesi Muhammet Bahattin BİNGÜL
Harran Üniversitesi Diş Hekimliği Fakültesi Ağız ve Diş Çene Cerrahisi, Orcid No: https://orcid.org/0000-0002-6581-2363

Oral cancer, is a subtype of head and neck cancer and is any cancerous tissue found anywhere in the oral cavity (1). However, since oral cancers are highly in the type of squamous cell carcinoma, this term directly describes oral squamous cell carcinoma that develops in the oral mucosa (2). Oral cancers can occur anywhere in the mouth, while cancers in adjacent anatomical structures such as the nose and sinus extend to the oral cavity or originate from the distant part of the body and metastasize to the mouth area.

Different histological types of oral cancers are possible, they can be listed as follows:

a) Adenocarcinoma and teratoma caused by the major or minor salivary glands

b) Lymphoma consisting of tonsils or other lymphoid tissues

c) Melanoma that occurs from the pigment producing cells of the oral mucosa.

Oral cancers with tongue involvement can be observed in the cheek, floor of the mouth, gums or palate. Under the microscope, it appears as a high rate of squamous cell carcinoma, it is malignant and spreads rapidly (3).

Small salivary glands in the oral cavity produce secretion that helps us swallow food and keeps our mouth wet (4). These cancers that can originate from minor salivary glands can also originate from superficial epithelial and squamous cell tissues, neurovascular structures, bone or dental structures (3). We can also call oral cancers as oral squamous cell carcinoma. Squamous cell carcinoma, which is mostly observed in the tongue and floor of the mouth, accounts for more than 90% of all oral cavity carcinomas (5,6). The remaining 10% consists of minor salivary gland-derived tumors, melanoma lymphoma and sarcomas (1).

If the definition of cancer is made more scientifically;

The cancer;

a) Since there is a rapid development in the cell, the cells develop abnormally and are distorted (anaplasia)

b) Transformation of the tissue cell into another cell (metaplasia)

c) Different from the tissues of origin (atypism)

d) Differing in shape (pleomorphism)

e) Development without being dependent on any organ (autonomy)

f) Continuous spreading without the end of development (invasion)

g) Abnormal mitotic activity (rapid development)

h) It is called a pathological condition that shows many criteria for malignancy, such as the absence of a fibrous capsule (3).

Almost all types of cancer have the ability to metastasize to the oral region (7). However, breast, lung, kidney, prostate, thyroid gland, uterus and colon cancer are primary tumors that metastasize more to the oral region (8-9). However, oral cancers mostly start in the cells lining the oral mucosa. Lips, tongue and floor of the mouth are the most common places (3). We can say that dentists are the most effective group that can make early diagnosis of oral cancers in terms of their location. Therefore, dentists should be careful and take a good anamnesis during the oral examination.

Epidemiology of Oral Cancers:

It is the 6th most common cancer in humans and the oral region has been reported to be the third most common cancer among men in developing countries (10). According to estimates made based on 20 different geographical regions in the world, it is claimed that there were 10.9 million new cancer cases in the world in 2002 and 274,000 of them were oral cancer cases, two thirds of which were men (11).

Our country is not sufficient to archive records in Turkey is difficult to reach because of exactly clear information about cancer incidence. Turkey in the list of notifiable diseases were cancer in 1982, and this statement on the Ministry of Health's Cancer Battle notification was requested to be made to the Department (12). However, as of 1999, reporting rates are between 35-40 per 100,000 people. The actual frequency estimates are that this number is between 150-200 per 100,000 people, that is, around 100,000 new cases are diagnosed annually (12-13). The World Health Organization data states that the annual cancer frequency is 260 per 100,000 in developing countries, while this rate is 102 per 100,000 in developing countries. There are predictions that the increase in the elderly population, especially in developing countries, will also increase in the number of cancers (13).

Oral cancer is the most common type of cancer in India and its incidence is up to 40% (14).

If we assume that only one third of all cancer cases have been treated in recent years, we can say that more effective diagnosis and treatment methods are urgently needed (3).

In a study conducted in Turkey between the years 1998-2004 is 231 oral cancer patients were examined 162 patients were male (70.1%), 69 women (29.9%) were reported to be. Of the 36 patients with lip cancer, 94.4% were men, 5.6% were women, 56.5% of 92 patients with tongue cancer were male, 43.5% were women, and 79.4% of 34 patients with floor cancer were male, 20.6% were female, 75% of 12 patients with gingiva and retromolar region cancer were male, 25% were female, 37% of 37 patients with tonsil cancer were male, 19% were female, 50% of 20 patients with buccal cancer were male,% 50 of them stated that they were women (15).

Oral cancers are seen with a high rate in the elderly. While oral cancers were seen in 10 of 100,000 people in the USA in 1995, their incidence in women was 6.0 in 100,000 and in men it was 14.7 in 100,000. Whilst the incidence is 9.8 per 100,000, it is higher for blacks at 12.3 per 100,000 The highest incidence is 20.6 per 100,000 in black men, while this figure is 14.2 per 100,000 in white men (16).

When all factors are considered, we can say that age is the highest risk factor for oral cancers. Oral cancer is a disease of those aged 40 and over, less common in young people. We can say that approximately 90% of all oral cancers are observed in individuals over the age of 40. The average age of patients diagnosed with oral cancer is over 65 years old. The importance of this factor is the increase in cancer prevalence. Because the population over the age of 65 in the USA is over 30 million, or in other words, it constitutes 13% of the total population. It is expected that the population over the age of 65 will rise over time and will constitute approximately 1 in 5 of the entire population in the USA by 2030. In addition, the population over the age of 65 has increased dramatically in the last decade compared to the rest (2).

The Etiology of Oral Cancers:

Smoking is one of the main factors in the development of oral cancers. Individuals who smoke or use a pipe have a high risk of developing cancer in the larynx, lungs, esophagus, kidneys, bladder or various other organs, as well as in the mouth or throat. Individuals with bad habits such as the use of pipes are highly likely to develop cancer in the lip area corresponding to the handle of the pipe. It is important for individuals who have received oral cancer treatment to quit smoking. Otherwise, the rate of encountering a secondary cancer in the mouth, throat, larynx or lungs of patients who continue to smoke is high (4).

Smoking, chewing tobacco, and using alcohol pose a great risk for developing oral cancer. Smoking and alcohol addicts are 3-4 times more likely to develop oral cancer than non-users. Although the prevalence of oral cancers varies depending on the geographical situation and age, it is more common in people over the age of 40, although it can be seen at any age. The rate of occurrence in men is 2 times higher than in women. Excessive smoking combined with high alcohol use is a common story of rest in a patient with mouth cancer. It has been suggested that high alcohol consumption plays an active role in the absorption of carcinogens in cigarettes or the occurrence of nutritional disorders. In this way, the transformation of squamous cells into ‘squamous cell’ cancer cells becomes simpler (3). In fact, according to the claims of a study; reported that the risk of oral cancer is 13 times higher in those who use alcohol and cigarettes together than those who use alcohol alone or smoke alone (17).

Since oral cancers take time to develop, the incidence in young people is low. Although most patients are over the age of 40-50 when they are first diagnosed with cancer, this has recently changed. It has been reported that cancers developing especially due to Human Papilloma Virus (HPV) are seen at a younger age (4). Since 1990, there has been an increase in the number of young patients under the age of 45 diagnosed with squamous cell carcinoma in the head and neck region. It was stated that the demographic information of this group of patients under the age of 45 is different from the etiological factors of cancer cases and what we know about gender. While HPV-related oral cancers are seen in men with a high rate of smoking and alcohol habits and with a good socio-economic status, tongue cancer is generally seen in young white women and the factors causing this condition are not fully known (18,19).

HPV has been reported in various studies to be involved in the development of cervical cancer in women and to be effective in oral cancers (20). HPV plays a role in the etiology of oral cancers, especially in the lingula and palatine tonsils of the oropharynx (21). HPV-16 and 18 are held responsible for the occurrence of all cervical cancers. It has also been stated that this virus is mostly transmitted through sexual intercourse in the USA. It has been claimed that the most suitable places for oral cancer in this group are the tongue base, tonsils, and oropharynx (3).

It is said that viral infections are effective in the development of oral cancers. Infective agents such as EbsteinBarr Virus (EBV) and Human Immunodeficiency Virus (HIV) rather than Human Papilloma Virus have been reported to have an effect on the development of oral cancers (22).

Some factors related to diet may play a role in the development of oral cancer. However, no characteristic dietary factors were found in individuals with oral cancer. Some experts suggest that poor dental health and unhealthy prostheses can lead to difficulty in chewing and therefore nutritional problems and pose a risk for oral cancers. However, there is no study to prove this assumption (2).

In a study conducted; They reported that the consumption of vegetables and fruits greatly reduced the risk of getting oral cancer, there was no relationship between consumption of red meat and salt and the possibility of oral cancer, and alcohol consumption increased the risk of oral cancer to a great extent. In the same study, they claimed that a diet lacking vitamin C also increased the likelihood of oral cancer (23).

The American Cancer Association recommends eating a plant-based diet. We can explain this diet by consuming at least 2.5 servings of vegetables and fruits every day. It is said that consumption of fresh vegetables and fruits reduces the development of oral cancer by 30-50%.

The presence of vegetables, citrus fruits, fish and vegetable oil in the diet is a shield against cancer. It is claimed that consuming whole grain bread and pasta instead of refined grains, fish and poultry and legumes instead of processed meat and red meat can also reduce the risk of cancer (24).

It is known that more than one factor is effective in the carcinogenesis of cancer. Although gene transitions are effective in cancer development, heredity explains only a part of all cancer causes. Changes in the gene and the proteins produced by these genes can change the biochemistry and functions of cells. At the same time, gene therapy can prevent these changes. The use of controlled cell proliferation and apoptosis can be an extremely critical approach in cancer treatment. The time needed for the cellular changes that cause cancerous tissue is extremely important, and the most important factor determining cancer susceptibility is age (2). The likelihood of the same cancer is increased 2-4 times in people whose close relatives have head and neck cancer, and this increase is more pronounced in people with known risk factors such as smoking and alcohol use (25).

Lower lip cancers may occur due to sunlight. Especially, the majority of lower lip cancers are seen in elderly men working under the sun, such as farmers, fishermen and construction workers, and they manifest themselves 8 times more than women (2).

Oral cancer is very likely to develop in individuals with certain genetic syndromes such as Fanconi anemia and dyskeratosis congenita caused by hereditary defects in certain genes (4). The risk of developing head and neck cancer is 500-700 times higher. Head and neck cancer is seen in 14% of patients with Fanconi anemia when they reach the age of 40 (26). Low oral hygiene and the presence of trauma are said to be local predisposing factors for oral cancers (4,22).

Although so many factors are effective in the occurrence of oral cancer; oral cancers are defined as preventable cancers by the World Health Organization (27).

The Clinical Symptoms of Oral Cancers:

Lesions seen in the oral mucosa are generally benign in character, but can easily be confused with malignancy with a few changes. The opposite may occur in situations, and it may be considered benign and early malignant changes may be encountered. Some lesions may transform into malignant character, which is why these lesions are called premalignant lesions. The most common complaint learned as a result of anamnesis taken in a patient with oral cancer is a wound or irritation in the mouth. However, other group of patients have severe and persistent pain. Carcinomas that occur in the mouth area can develop painlessly or be associated with moderate irritation (2). Clinically diagnosing advanced

squamous cell carcinoma of the mouth is not very difficult. The intraoral image of advanced oral cancers appears as an ulcerated, raised nodule with an ulcerated surface or an irregularly raised edge, an amorphous ulcer with fibrin accumulation in the middle. When palpated, it can be felt to be fixed to the underlying tissues (28).

The most unfavorable situation we will encounter in the early stage of an oral malignancy is the absence of any subjective symptoms. There is no pain in these lesions in the early period, the patient may not have noticed a possible swelling, as well as the absence of bleeding and exudation, a white spot, hyperkeratosis, weak ulcer or fissures may appear as early findings in intraoral examination. We can list the places where we encounter the most oral malignancies as the lateral edges and ventral surface of the tongue, lower lip and buccal mucosa. These places should be palpated carefully. In oral cancers; Ulcers or bumps can be seen on the lips, tongue or other parts of the oral area, and even these lesions may appear as dark or pale spots. We may come across leukoplasia or erythroplasia as an early finding (3).

Due to the high probability of oral cancer, careful oral examination and knowledge of the symptoms are items that will guide the early detection of oral cancers. The survival rate of patients with oral cancer recognized before lymph involvement is 70% (29). Therefore, oral examinations are very important and in this sense, dentists have a great responsibility. In addition to taking a careful history, dentists should perform the examination of areas that can be missed such as the retromolar area, tonsillar fossa, posterior part of the tongue, floor of the mouth, palatinal part and oropharynx for early diagnosis (3).

In advanced oral cancer lesions; ulceration on the surface and fixation at the base. The mass is in the form of an ulcerated surface or an irregular ulcer with raised edges. Early oral cancers can be in the form of erythroplakia, leukoplakia and painless small ulcers (2).

To summarize, we can list the possible signs and symptoms of oral cancers as follows:

- Persistent and non-healing wounds in the oral area as the most common finding
- Presence of persistent pain in the intraoral region as another common finding
- A mass in the cheek or thickening in this area
- The presence of a white or red area on the mucous membrane of the gums, tongue, tonsils or intraoral area
- Burning or incessant tingling sensation in the throat

- Difficulty chewing or swallowing
- Restricted jaw or tongue movements
- Insensitiveness anywhere in the oral area
- Deterioration of the fit of the dentures in the jaw or swelling that causes discomfort
- Losses in the teeth or pain in the teeth with the jaw
- Sound distortions
- The presence of a lump or mass in the neck
- Losing weight
- Unpleasant odors in the breath

Some of these changes mentioned above may occur due to benign problems as well as other cancers of the region. If any of these symptoms persist for more than 15 days, it is very important to consult a doctor or dentist and determine the cause and treat it (4).

Histopathology in Oral Cancers:

They are mostly well or moderately differentiated cancers. Pathologists may have difficulty determining whether this cancer has differentiated, whether it is an anaplastic tumor. There are criteria for anaplasia in cells. Histologically, we can list them as follows:

a) Changes in the size and appearance of cells and nuclei

b) Increases in nuclei

c) Atypical mitosis

d) Hyperchromatism

e) Increases in the ratio of nucleus to cytoplasm (3).

Infiltration and ulceration is often present in a primary tumor of the oral mucous membrane. While squamous cell carcinomas are seen in the palatine, adenocarcinomas originating from the salivary gland and mucoepidermoid carcinomas are frequently encountered here. These lesions can be confused with abscesses or benign growths (29).

Staging in Oral Cancers:

The more important the cancer diagnosis is in a patient, the more important it is to know the stage of the cancer diagnosed. It may be necessary to apply a different treatment protocol for cancers of the same organ at different stages. At the same time, a staging system is needed to have information about the prognosis of the cancerous tissue, to choose the

appropriate treatment plan for that patient, and to evaluate the results in the light of the literature. By staging the disease, in addition to using a common terminology, a language that everyone can understand is emerged (30).

In order to report cancer and its results, it has developed the TNM staging system defined by the American Joint Committee on Cancer staging. T refers to the size of the lesion. N indicates the number, size and location of the nodal involvement and its subtitles. M indicates whether there is distant metastasis and its number. Although the TNM staging system provides information about the conditions we have just mentioned, it does not always have a determining value in terms of survival and prognosis and does not give precise and clear results about prognosis (5).

Depth of invasion, degree of differentiation and other histopathological features, which have an important place in the prognosis of oral cancers, are not included in this classification (31). Parameters such as lymph nodes in the neck, extracapsular extension, fixation and whether the lymph node is cystic or not, which were considered only in terms of size and number, were not included in the classification. Despite the above criticisms, TNM staging provides valuable information while determining the prognosis of a cancerous lesion. For all types of oral cancers, the stage of the lesion, the state of the neck, and whether it has metastasis affect the prognosis with statistically significant data (5).

Diagnosis and Treatment in Oral Cancers:

Despite major advances in the diagnosis and treatment of oral cancers in recent years, half of the patients die in the first five years. Individuals with oral cancer have one of the five lowest survival rates. The survival rate can be increased to higher values with early diagnosis and effective treatment (32).

Except for oral and skin cancers, there is no other type of cancer that can be suspected or even diagnosed only with an eye examination (33). Although it is visible, it is often not diagnosed early (33,34). Early diagnosis is one of the main factors affecting survival rate in oral cancer cases. However, the diagnosis may be delayed due to the delay of patients in applying to their physicians or the inability of the physicians to distinguish the lesions they encounter (33).

Toluidine blue is a metachromatic agent from the thiazine group and is thought to work by staining the nucleic acid inside the cell nucleus due to its ability to bind to DNA. Toluidine blue confirms increased cancer activity in lesions with a risk of malignancy. In addition, the biopsy sample to be taken from suspicious lesions also helps in determining the area. A study was conducted on 169 patients who were thought to have premalignant or malignant oral lesions to investigate the reliability of this technique by a

researcher named Silverman. In the study, first the lesions were stained with toluidine blue and then biopsy was taken with the traditional method. Histopathological evaluation revealed squamous cell carcinoma in 62 patients, epithelial dysplasia in 13 patients, and benign mucosal changes in 94 patients. He claimed that the overall accuracy rate of toluidine blue was over 90%. As a result, staining vital tissues with toluidine is important in early diagnosis. In addition, it accelerates the biopsy process and enables a careful examination, as well as a useful clinical judgment and the selection of the most appropriate area to biopsy (2).

We can benefit from biopsy in the diagnosis of oral cancers. Biopsy is the name given to the process of taking a piece from the lesion and sending it to the pathologist in order to make a clear diagnosis of any lesion. For lesions that do not heal in more than 15 days and for which we do not have information about their pathology, biopsy is a must. Before proceeding to the biopsy procedure, a complete history of the lesion should be taken and its appearance should be described in detail. With biopsy, we can make a clear diagnosis of the lesion, obtain information about the prognosis of the lesion, confirm the wrong clinical diagnosis, and save the patient from fear of cancer by learning the clear diagnosis. When performing the biopsy procedure, we should always do it carefully, including the living tumor tissue, provided that it is at a sufficient depth right from the center of the lesion. Spilled, infected, necrotic surface of the material should not be included. After the biopsy is taken, the area where the mass is sent to the pathologist should be explained, and the clinical and radiological findings should be sent in 10% formalin (3).

There are many techniques in biopsy procedures other than incisional, curettage and punch biopsy methods. If we briefly talk about these methods;

a) Incisional Biopsy: It is a type of biopsy performed by taking a "V" shaped sample from the healthy and diseased part of the lesion. If the lesion is large and there are areas of different characters on the lesion, it is useful to take more than one sample (2).

b) Excisional Biopsy: Although it is the most reliable method, it is the process of removing the lesion completely and sending it to the pathologist. It is beneficial to remove it with some intact tissue around.

c) Punch Biopsy: We can define it as the process of removing parts from intra-bone lesions by piercing the bone.

d) Aspiration Biopsy: It is a technique performed as fluid aspiration from body cavities or cysts.

e) Silver Needle Biopsy: It is a method mostly preferred in deep lesions.

f) Electrosurgical Method: It is preferred in lesions with high bleeding risk (3).

g) Cytological Smear: It is a diagnostic method performed by collecting cell samples from all epithelial layers from the oral mucosa surface with a specially designed brush (2).

When patients who may have oral cancer apply to a physician, it should be recommended to perform the examinations and tests listed below:

Inspection Methods and Tests:

- Medical history and physical examination
- Head and neck assessment
- Indirect pharyngoscopy and laryngoscopy
- Panendoscopy

-Biopsy

-Viewing Methods

- Chest film
- Computed tomography
- Magnetic resonance imaging
- Positron emission tomography
- Swallowing Barium
- Blood tests

The data we will obtain as a result of these techniques can be used alone or in combination depending on the region and stage of the tumor (4).

The main two options in the treatment of oral cancers are surgery and radiotherapy, or the combination of both. Surgical method is mostly preferred as a treatment option in small carcinomas that can be excised, especially in carcinomas with bone infiltration and in cases where radiotherapy has not been successful (35). Treatment of oral cancers with radical surgery is directed to 2 main areas. The first one is the surgical treatment of the tumor, the second one is the treatment of hidden prominent neck metastases. Therefore, in the surgical treatment of these patients, mostly the resection of the primary tumor and various forms of neck dissections accompany the surgery (36).

Radiotherapy is a preferred treatment option of ionizing radiation for cancer and specified non-cancer diseases. It is aimed to apply the previously calculated ionizing radiation dose to the predetermined tumor

volume in radiotherapy treatments in a way that will cause as little damage to the healthy tissues surrounding the tumor tissue (36).

In curative treatment applications, it is aimed to increase the quality of life of the treated patient and increase the chance of survival by eliminating the tumor volume (37).

Radiotherapy external and brachytherapy applications can be performed by two different methods in the treatment of patients diagnosed with oral cancer (37). External radiotherapy is performed by delivering beams from outside to patients at a distance, and brachytherapy is performed by placing the radiation source directly on the tissue containing the tumor to be treated (36).

The methods we will use in the treatment of oral cancers are surgery, radiotherapy and chemotherapy. While establishing a patient's treatment protocol, the general condition of the patient, the type and stage of the cancer, the probability of the treatment option we will choose to be beneficial, and the possible effects of the treatment on important functions such as phonation, chewing and swallowing should be evaluated (4).

Since oral cancers are in an area where dentists work constantly, dentists have certain responsibilities. Because early diagnosis of oral cancers will seriously affect the survival rate of patients.

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Chapter 23

GENITOURINARY TRAUMAS

Muhammed EKMEKYAPAR[1]

1 [1]Malatya Education and Research Hospital, Department of Emergency Medicine

INTRODUCTION

Trauma-related injuries create severe problems in terms of health and constitute serious life threat. An examination toward the deaths in the United States of America (USA) indicated that every one of fourteen deaths arose from injuries (Paparel et al., 2006). Trauma is the first cause of death among the people at young ages. The renal and urogenital system have the organs that are affected by the trauma-related injuries the most (15%), and urogenital injuries are generally accompanied by other organ injuries in the abdomen (Olmez, 2016).

Organs of the urinary system are different from other solid and hollow organs, as these organs form urine (kidneys), carry the urine (ureters and urethra) or store urine (bladder) (Gross, Lehnert, Linnau, Voelzke, & Sandstrom, 2015).

Genitourinary system traumas constitute approximately 10% of all trauma cases (Chouhan, Winer, Johnson, Weiss, & Hyacinthe, 2016). Abdominal traumas can be examined as blunt and penetrating traumas. Blunt abdominal traumas reflect the traumas in the organs within the abdomen without distorting the abdominal wall. These traumas generally occur as a result of motor vehicle accidents, falling and violence, with the traffic accidents being as the most common cause (Degirmentepe, Polat, & Otunctemur, 2017). Penetrating traumas result in the distortion of abdominal wall; additionally, these traumas generally occur owing to firearm and sharp object injuries. Penetrating injuries display a more severe clinical course compared to the blunt injuries (McAninch, 1999).

Traumas and particularly traffic accidents are the most important causes of mortality and morbidity among the young population in Turkey and other countries. The first centers patients apply to for their traumas are emergency ambulances and emergency services patients reach by their own. These patients are regarded as multiple trauma in the emergency services, and their physical examinations, radiological screenings and treatments are planned accordingly. After performing the physical examinations in the emergency services, patients' vital and clinic signs are stabilized, and they are radiologically examined with more focus on the details. Moreover, tetanus prophylaxis and anti-biotic treatment are initiated if necessary. If patients have open wounds, these wounds are sutured. In the event that there are any potentially life-threatening cases or an injury requiring surgical treatment or hospitalization, necessary consultations are requested. Patients may need to undergo surgical procedures or hospitalization, or they are discharged following a certain period of monitoring is they have a minor trauma.

Urinary system consists of kidneys, ureters, bladder and urethra. Male genital system includes penis, scrotum, testicles, epididymis and prostate, while female genital system consists of vulva, vagina, uterus, tubal tubes and ovaries. Main function of the urinary system is to filter the wastes in the blood through both kidneys, to carry these wastes to the bladder via the ureters, and to discharge the wastes as urine through the urethra. The main function of the genital system, however, is to reproduce.

This study detailed the urogenital traumas which constitute a certain rate of all traumas with a general approach toward the trauma cases.

GENERAL APPROACH TO TRAUMA PATIENT

As noted earlier, trauma is the most important cause of morbidity and mortality among young patients. Traumas can be assessed under two main categories as blunt and penetrating traumas. Blunt traumas result from motor vehicle accidents and falling from a high point while penetrating traumas occur following the injuries from sharp objects and firearms. The blunt traumas mainly result from traffic accidents. Motor vehicle accidents, falling from a high point and similar accidents may all cause blunt traumas, some of which can be minimized by being careful and taking simple precautions. Despite these actions, traumas are still a severe issue in Turkey and other countries.

Trauma patients should be treated in emergency services with experienced and equipped crews. Presence of a surgeon team is a plus point. People who primarily manage these patients from the beginning to the end are emergency medicine specialists. After the primary examinations are performed by these specialists, the surgery team needed for the monitoring and treatment processes is established. Surgeons from the necessary surgical branches are included along with the emergency medicine specialists to the team. The surgical branches needed the most for the multiple traumas are neurosurgery, general surgery and orthopedic surgery. If patients have thoracic trauma, thoracic surgery expert should be included. Moreover, if vascular injuries are present, a cardiovascular surgeon should be added to the team, and if patients have a urogenital injury, a urological surgeon should be included. Other than these branches and experts, a plastic and otorhinolaryngology expert and an ophthalmologist should also be added to the team.

The first units trauma patients apply to are generally emergency services which are equipped with necessary materials and instruments to manage multiple trauma cases. Our objective regarding the trauma patients is to make a diagnosis and perform the treatment as soon as possible. What should be done first when these patients apply to emergency services

is to make the patients lay on the trauma board and wear a cervical collar, and to establish vascular access on two locations simultaneously. Then, the general physical examination should be conducted. The first physical examination is called the primary examination which is performed to determine whether a life-threatening case is present for the patient. During this process, patient's vital signs such as blood pressure, pulse, body temperature and oxygen saturation level are recorded, and patient's Glasgow Coma Scale (GCS) value is assessed. If the patient's condition is stable following the primary examination, meaning if the patient is conscious and have normal vital signs, necessary radiological screenings are performed. However, if the patient is not stable, these screenings are performed after stabilizing the patients. Three locations called three spaces, which are the brain, thorax and abdomen, should be clearly and meticulously examined. Following the primary examination and radiological screenings, a detailed secondary examination should be performed. If the patient have wounds, medical dressing and suturation (if necessary) should be conducted, and tetanus prophylaxis and anti-biotic treatment should be initiated. Any potentially life-threatening cases are determined following these assessments, and necessary consultations are requested for the cases found following the examination and radiological screenings. If a surgical operation is planned, extra blood is supplied for the patient and operating room and patient are prepared for the emergency surgery. If the patient still needs to be hospitalized despite the absence of the need for emergency procedure, necessary transactions are performed and the patient is directed to the relevant clinic. If the patient has no life-threatening risk and indications requiring hospitalization, the patient is discharged from the emergency service with suggestions after the control examination performed in accordance with the monitoring and treatment processes conducted in the emergency service for patient's trauma and after determining that the patient has no life-threatening risk, indications requiring hospitalization and any pathologic cases. If deemed necessary, a prescription is provided to the patient who is then suggested to apply to the relevant polyclinic for checks.

Trauma is a significant and detailed issue requiring multi-disciplinary approach and divided into many sub-categories. This study examined urogenital traumas, some of these sub-categories, as urinary system traumas and genital traumas.

URINARY SYSTEM TRAUMAS

Urinary system traumas can be assessed under four categories as renal, ureter, bladder and urethra traumas. If patients have a sign indicating the urinary system trauma, the abdominal system should be examined in detail for other organ injuries. If patients are brought to the emergency service as

a result of multiple traumas, they should be assessed accordingly. However, if there are isolated urinary system or abdominal trauma, the physical examinations based on the symptoms should guide us in this period.

1- RENAL TRAUMAS

Kidneys are the organs that are injured the most among the genitourinary organs (Morey et al., 2014). They are particularly vulnerable against injuries as they are solely fixed by renal pelvis and vascular pedicle in the abdominal cavity (Schmidlin, 1998). More than 80% of the renal injuries occur as a result of blunt traumas in USA (Santucci, 2001). Penetrating traumas are rare but they may result from more severe injuries (Mee, McAninch, Robinson, Auerbac, & Carroll, 1989).

Stages of renal traumas are presented in Table 1 (Santucci, & Doumanian, 2012). Laceration in liver and right kidney as well as the intra-abdominal free fluid which emerged following the multiple traumas are presented in Figure 1. The laceration in the left kidney of another case along with the intra-abdominal free fluid which arose from multiple traumas are present in Figure 2.

Table-1: Stages of renal traumas

Grade	
1	Most common. Contusion and parenchymal damage. Sub-capsular hematoma may occur with contusion
2	Parenchymal laceration extends through the cortex. Minor perirenal hematoma
3	Parenchymal laceration extends through the cortex and medulla. Retroperitoneal hematoma is broad
4	Parenchymal laceration extends through the collecting system. Bleeding related to renal arterial thrombosis and vascular injury
5	Ruptured kidney/fully torn renal pedicle

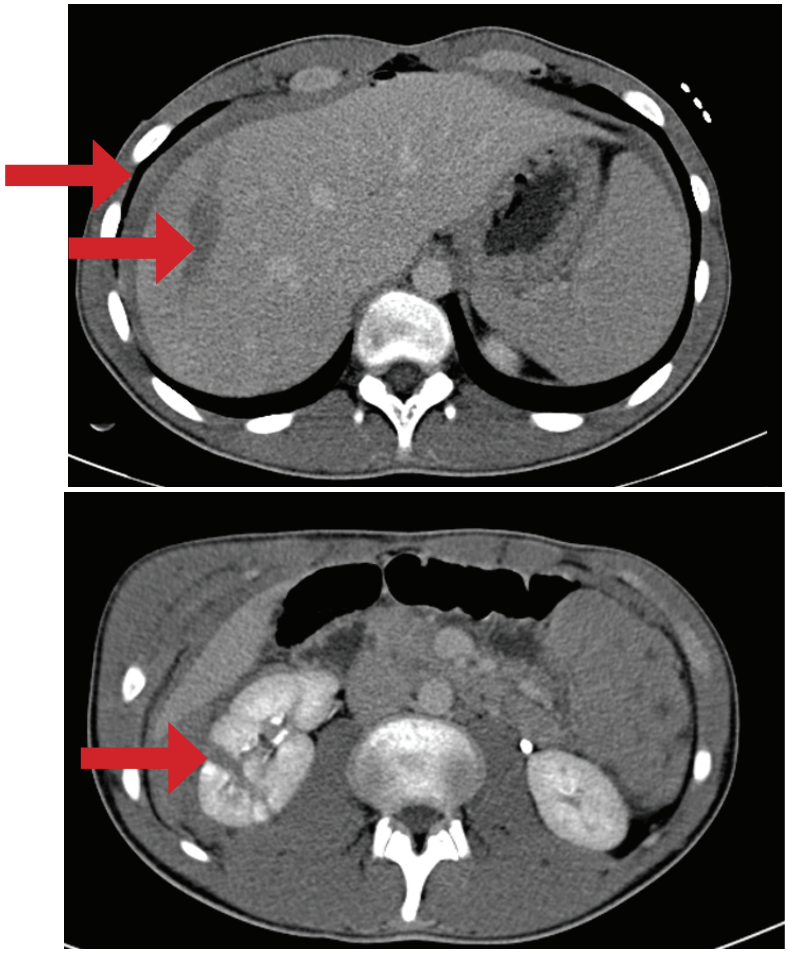

Figure-1: Laceration in the liver and right kidney along with the intra-abdominal free fluid

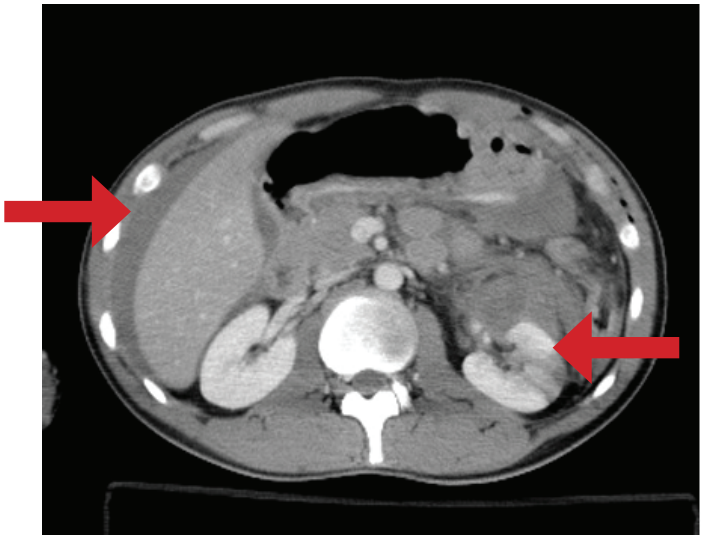

Figure-2: Laceration in the left kidney along with the intra-abdominal free fluid

Diagnosis

Entry/exit holes can be seen during the physical examinations of the trauma cases arising from firearm injuries. The strongest indicators of urinary system damages arising from traumatic injuries include hematuria, pain, ecchymoses, broken ribs and abdominal distention (Serafetinides (2015a)). A complete urinalysis and tests for the hematocrit and creatine levels are among the main tests to be done in these cases. Presence of hematuria is the indicator of renal damage but hematuria may occur not only due to renal damage, but also owing to the injuries in other urinary organs. However, absence of hematuria does mean that a major injury is not present (Hoke et al., 2007).

Computed tomography is used as the accurate specific screening method to detect the urinary system damages and comorbid intra-abdominal injuries among trauma patients (Bittenbinder, & Reed, 2013). Penetrating injuries in the abdominal area may result in clinically-severe conditions; these patients should be radiologically assessed without regard to the degree of hematuria (Serafetinides, 2015). Moreover, computed tomography is also effective for the assessment of firearm injuries for which a surgery is not planned (Velmahos, 2005).

Ultrasonography (USG) guides experts in terms of whether patients need a detailed check and is beneficial for clinical monitoring (Gaitini, Beck-Razi, Engel & Dogra, 2008).

Intravenous pyelography (IVP) is not as effective as computed tomography for assessing patients (Morey, 1999).

Treatment

What should be done first is to check the vital signs and stabilize patients clinically, which is to be done for every trauma case. The treatment is then planned based on the clinical conditions of patients and organ injuries. If the clinical conditions are normal and patients are stable, then the patients are monitored until the hematuria ends following the blunt renal trauma. Patients are told to rest on bed and treated with prophylactic anti-biotic; vital signs are continuously followed (Olmez, 2016).

Controlling the bleeding and saving the kidney is the main objective of surgical treatment. The indications of surgical treatment include changes in patients' hemodynamic values, necessity of surgical procedures for other organ injuries, expanded perirenal hematoma in the laparotomy or pulsation, and fifth-grade renal damage (Santucci, & Doumanian, 2012).

With the quick physical examinations; urinalysis and necessary radiological assessment should be conducted and vital signs and renal function values should be followed. The monitoring should continue until the full recovery occurs (Akbulut & Tunc, 2016).

2- URETER TRAUMAS

Ureter trauma is the rarest genitourinary trauma form owing to the small sizes of ureter and its dynamic and protected location. The most common cause of ureter injuries is iatrogenic traumas (Summerton et al., 2015; Summerton et al., 2012); additionally, blunt and penetrating traumas constitute less than one-fourth of all ureter injuries (Palmer, Rosenbaum, Gershbaum, & Kreutzer, 1999). The most frequently injured location of ureter is the sub 1/3 area (Palmer, Rosenbaum, Gershbaum, & Kreutzer, 1999). Ureter injury severity is classified according to the American Association for the Surgery of Trauma (AAST) as follows (Bryk, & Zhao, 2016): presence of hematoma grade-1, laceration around the ureter that is smaller than 50% grade-2, laceration around the ureter that is greater than 50% grade-3, full-layer rupture and devascularization smaller than 2 cm grade-4, and full-layer rupture and devascularization greater than 2 cm grade-5.

Diagnosis

Making a diagnosis for the ureter injuries is difficult because these injuries do not display specific signs and symptoms. Presence of hematuria is a weak indicator of ureter traumas because hematuria is observed only among the half of ureter traumas. Traces of bullets or knives should be examined in all patients with penetrating traumas who are doubted to have a ureter injury, and they should be evaluated in this regard (Olmez, 2016).

Treatment

Management of ureter trauma is based on the structure, severity and location of the wound. The standard of the external trauma is surgical correction (Serafetinides, 2015). Proximal and urethral injuries in the middle sections are treated with primary ureteroureterostomy, while distal injuries are generally treated with urethral re-implantation (Degirmentepe, Polat, & Otunctemur, 2017).

3- BLADDER TRAUMAS

Bladder traumas are generally related to pelvic fractures (Sandler, Goldman, & Kawashima, 1998). Severity of bladder injuries is assessed through the AAST organ injury scale (Table-2) (Bryk, & Zhao, 2016). External traumatic bladder injuries are rare and seen in less than 2% of patients who have been operated for abdominal trauma (Carroll, & McAninch, 1984; Gomez, 2004).

Table-2: Severity of bladder injuries AAST organ injury scale

Grade	
1	Hematoma-contusion, laceration at partial thickness
2	Laceration of extraperitoneal bladder wall smaller than 2 cm
3	Laceration of extraperitoneal bladder wall greater than 2 cm or laceration of intraperitoneal bladder wall smaller than 2 cm
4	Laceration of intraperitoneal bladder wall greater than 2 cm
5	Intraperitoneal or extraperitoneal bladder wall laceration extending through the bladder neck or urethral entry

Diagnosis

The indicators suggesting bladder injuries include macroscopic hematuria, sensitivity in the abdomen, failure to urinate, suprapubic bruises, and extravasation of urine resulting in distension in the abdomen, swelling in perineum, scrotum and frontal abdominal wall (Djakovic et al., 2005). Regular or CT cystography performed with the opaque substance in the bladder which reaches the volume of 350 ml occasionally is a diagnostic method. CT cystography can also reflect the simultaneous pelvic or abdominal injuries (Figler et al., 2012; Gomez et al., 2004; Shenfeld, & Gnessin, 2011).

Treatment

- Conservative treatment: Patients are clinically monitored; what should be observed in this period is hematuria and sepsis. They are treated with a catheter and monitored for 7-14 days, and their recovery is observed with the continuous cystography sessions performed following the bladder drainage. After these steps, anti-biotic prophylaxis is initiated (Olmez, 2016).

- Surgical treatment: Repair through open surgery should be performed in cases of intraperitoneal rupture, bladder injuries arising from penetrating trauma, iatrogenic injuries and co-morbid organ injuries. Following the procedure, a 10-day catheterization process will be sufficient (Olmez, 2016).

4- URETHRA TRAUMAS

Urethral injuries may occur as a result of blunt trauma, iatrogenic injury and penetrating trauma. These injuries are more common among men as male urethra is longer than that of women. In the blunt pelvic trauma cases, blood in penile meatus, perineal contusion, urinary retention and displaced or moving prostate indicate urethral injuries, and retrograde urethrographic screening should be performed in this case (Degirmentepe, Polat, & Otunctemur, 2017). According to AAST, urethral injury scale is classified as follows (Djakovic et al., 2005): Blood in urethral meatus along with contusion despite normal urethrography result grade-1; strain injury, extension of the urethra without extravasation in urethrography grade-2; partial rupture, contrast extravasation from the injured area while revealing contrast substance in the bladder grade-3, full rupture, contrast extravasation from the injured area without revealing contrast substance in the bladder, urethral separation smaller than 2 cm grade-4; and full-layer rupture, urethral separation greater than 2 cm, trans-section or extension to prostate or vagina grade-5.

Diagnosis

Retrograde urethrography This method is the golden standard for assessing urethra injuries among men. The localization, dimension and severity of the injury can be determined (Olmez, 2016). Extravasation can be seen when the contrast substance reaches the bladder in incomplete ruptures. Presence of extravasation without the access of contrast substance to the bladder suggests complete rupture (Ozgok, & Seckin, 2002).

Ultrasonography: This method is not commonly preferred but it may be used in cases where suprapubic catheter is to be used (Srinivasa, Akbar, Jafri, & Howells, 2009).

CT and MRI: These are not routinely preferred in the emergency assessments. However, they are quite useful in monitoring other intra-abdominal organ injuries (Olmez, 2016).

Treatment

Partial urethral ruptures can be non-surgically managed with suprapubic or urethral catheter, but tightness may occur following a minor risk. Total rupture of the urethra is surgically treated (Ingram, Skippage, Watson, & Patel, 2008; Rosenstein, & Alsikafi, 2006).

GENITAL TRAUMAS

Genital organs are generally related to reproduction. Injuries for these organs should be assessed with the urinary system. Both urinary and genital systems work collectively.

The most common injuries concerning the external genital area include penile fracture, testicle rupture and penetrating penis injuries (Bryk, & Zhao, 2016). If there is blood or hematuria in the urethral meatus, the case should be assessed considering the urethral injury along with the external injury (El-Assmy, El-Tholoth, Mohsen, & El Housseiny, 2011; Wang et al., 1995).

This study reflected the genital traumas under three categories as the most common forms of genital traumas: penis, scrotum/testicle and vulva-vagina injuries.

1- PENIS TRAUMAS

Penile fracture is the most common blunt trauma for penis and occurs when erected penis is bended during sexual intercourse, masturbation, falling from bed when the penis is erected or trying to ensure detumescence by hand (Olmez, 2016). According to AAST, severity scale for penis injuries is as follows (Djakovic et al., 2005): Contusion/laceration on the skin grade-1, Buck's facia laceration without tissue loss grade-2, presence of avulsion/laceration with glans/meatus/cavernosal or urethral defect smaller than 2 cm on the skin grade-3, cavernosal or urethral defect greater than 2 cm / partial penectomy grade-4 and presence of total penectomy grade-5.

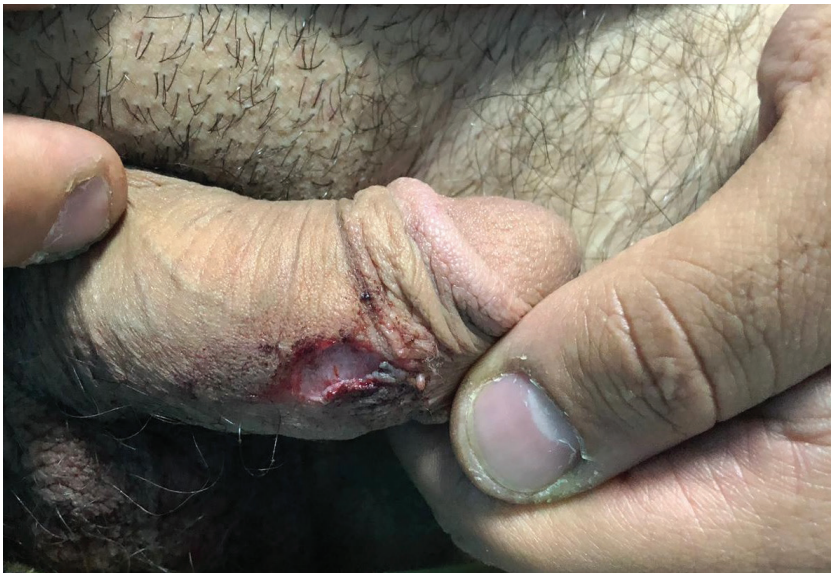

Figure-3: Penile injury

Diagnosis

The diagnosis of penile fracture is made following the anamnesis and physical examination. The penis is deviated in the reverse position of the fracture due to the hematoma (Olmez, 2016).

Treatment

The hematoma is urgently discharged and the laceration in the tunica albuginea is repaired (Serafetinides (2015b)). Surgical exploration and primarily suturing the necrotic tissue via debridement is recommended for most of the penetrating penile traumas (Djakovic et al., 2005).

2- SCROTUM AND TESTICLE TRAUMAS

Scrotal injuries may occur as blunt and penetrating injuries. A strike to the crotch, getting struck by a ball during a sports activity, or falling on the scrotum like mounting a horse are among the causes of blunt scrotal traumas. Penetrating injuries occur as a result of sharp objects or getting shot (Olmez, 2016). Severity scale of scrotum injuries according to AAST is as follows (Djakovic et al., 2005): Presence of contusion grade-1, laceration less than 25% of the scrotal diameter grade-2, laceration greater than 25% of the scrotal diameter grade-3, presence of avulsion smaller than 50% grade-4 and avulsion greater than 50% grade-5.

Severity scale of testicle injuries according to AAST is as follows (Djakovic et al., 2005): presence of contusion or hematoma grade-1, sub-clinic laceration in tunica albuginea grade-2, loss of parenchyma less than 50% along with the laceration in tunica albuginea grade-3, major laceration along with parenchyma loss at %50 or higher grade-4 and total testicle damage and presence of avulsion grade-5 (Bilateral lesions are increased one degree until the Degree 5).

Diagnosis

The scrotum is swollen and painful in the physical examination. The entry-exit points owing to firearm injuries can be seen in the scrotum. Color doppler ultrasonography should be used to assess the integrity of the testicle and blood flow in the scrotum (Olmez, 2016).

Treatment

The treatment to be used for minor injuries include bed rest, cold application, analgesic medication, prophylactic anti-biotic and scrotal elevation; these are sufficient for treating minor injuries. However, if the degree of the injury is severe, (such as erosion, laceration or tissue loss) the scrotal area should be initially washed with saline solution and dressed with anti-septic solutions, and then the anti-biotherapy should be started. Following the debridement, skin of scrotum should be sutured (Olmez, 2016). If patients have rupture in their testicles, emergency surgical

exploration and primary testicular repair are needed; moreover, delays in the surgical actions to be taken in these cases make the process of saving testicles difficult (Buckley, & McAninch, 2006). The case with the ruptured right and left scrotum and right testicle who was brought to the emergency service with multiple traumas following a motor vehicle accident and who was operated urgently is presented in Figure-4.

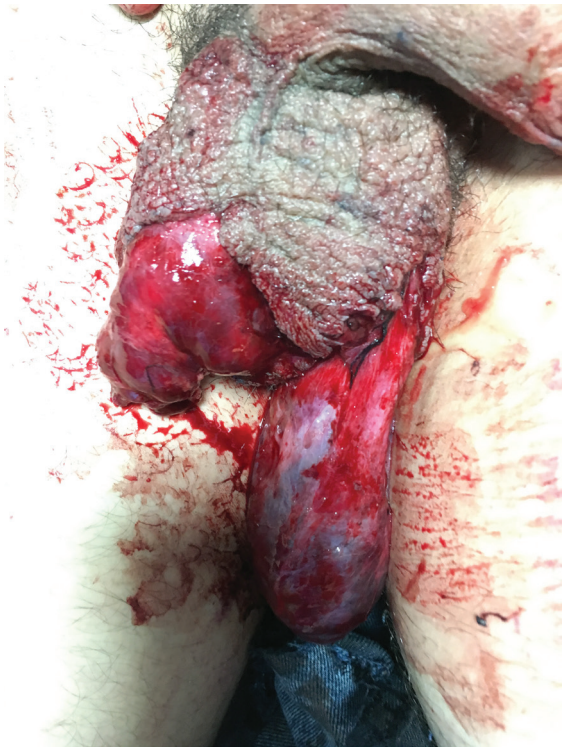

Figure-4: Ruptured right and left scrotum and right testicle

3- VULVA and VAGINA TRAUMAS

Diagnosis

Gynecological examination is necessary for women who have genital injuries or blood in the vaginal area (Djakovic et al., 2005).

Treatment

Hematoma often emerges in the vulva in blunt traumas; use of non-steroid medications and ice bags generally relives the pain. Surgical procedure may be needed for the patients who have common vulva hematoma or who are not hemodynamically stable. Following the conservative debridement, repair is needed for vulva lacerations. Severity scale regarding the vulva and vaginal injuries according to AAST is presented below (Table-3, Table-4) (Djakovic et al., 2005).

Table-3: Vulva injury severity scale (adapted from AAST)

Grade	Definition
1	Contusion or hematoma
2	Laceration, superficial (only on the skin)
3	Laceration, on deep fat tissue or muscle
4	Avulsion, on the skin, fat tissue or muscle
5	Injury in the neighboring organs (anus, rectum, urethra, bladder)

* Bilateral lesions are increased one degree until the Degree 5

Table-4: Vagina injury severity scale (adapted from AAST)

Grade	Definition
1	Contusion or hematoma
2	Laceration, superficial (only on the mucosa)
3	Laceration, on deep fat tissue or muscle
4	Laceration, complicated, in the cervix or peritoneum
5	Injury in the neighboring organs (anus, rectum, urethra, bladder)

* Bilateral lesions are increased one degree until the degree 5

Trauma is a broad term but urogenital traumas were briefly explained in this study. The most important aspect to be understood from this study is that patients applying due to a trauma should be comprehensively assessed as multiple trauma case and systemic examination should be carried out properly.

The objective regarding the patients hospitalized due to multiple trauma is to stabilize them if their general conditions are poor. If the airway patency cannot be protected and patients' GCS values are low (<10 for trauma cases), these patients should be intubated. After stabilizing the patients, necessary radiological assessments should be asked based on patients' physical examinations. Moreover, open wounds should be dressed clearly and sutured if necessary. The actions that should not be forgotten during this process is to ensure tetanus prophylaxis and start antibiotic treatment following the necessary questioning session.

The radiological tests demanded in line with the status of the trauma should be assessed as soon as possible, and the life-threatening problems should be considered first. Brain, thoracic and abdominal injuries are among the life-threatening injuries; accordingly, any injuries and traumas in these areas should be assessed in detail. In addition, using the bedside fast ultrasound, the abdomen and thorax can be assessed until the patient is stabilized. Fast ultrasound is one of the most important radiological screening methods used in the emergency services to monitor patients in the present time as it can be used next to the patients and repeated, and as it does not require much time. Fast ultrasound can reveal the details about solid organ injuries in the abdomen, intra-abdominal free fluids, and

hollow organ perforations. Moreover, fast ultrasound can be used to assess the thorax for pneumohemothorax, and to evaluate the pericardial window for pericardial fluids and tamponade.

CONCLUSION

Trauma is a severe cause of morbidity and mortality for the patients at all ages, particularly for the young patients. All trauma cases other than the isolated minor traumas in the emergency services should be assessed as multiple trauma; that is, trauma patients should be holistically assessed. Patients' all systems should be examined, and their entire bodies should be screened if needed. Following the primary examination phase for the patients who are hospitalized owing to blunt traumas such as motor vehicle accidents or falling from a high point, a meticulous secondary examination should be performed. In addition, it should be remembered that patients who are brought for isolated and multiple traumas or abdominal traumas may have injuries in their urogenital systems. Presence of hematuria in these patients should be an alerting sign for us, and renal, ureter or urethra injuries should be considered. If no contraindication is present, foley catheter should be used for these patients, and urine flow and hematuria should be monitored.

Following the stabilization and radiological screenings, necessary consultation should be demanded. In addition, surgical procedures should be planned and the operation should be initiated as soon as possible if necessary. If patients are to be hospitalized despite the absence of the need for a surgery, patients should be directed to the relevant clinic following the necessary consultations after the transactions in the emergency unit end. If there is no medical need to hospitalize these patients, they can be discharged with the necessary suggestions and information after the observation in the emergency service ends.

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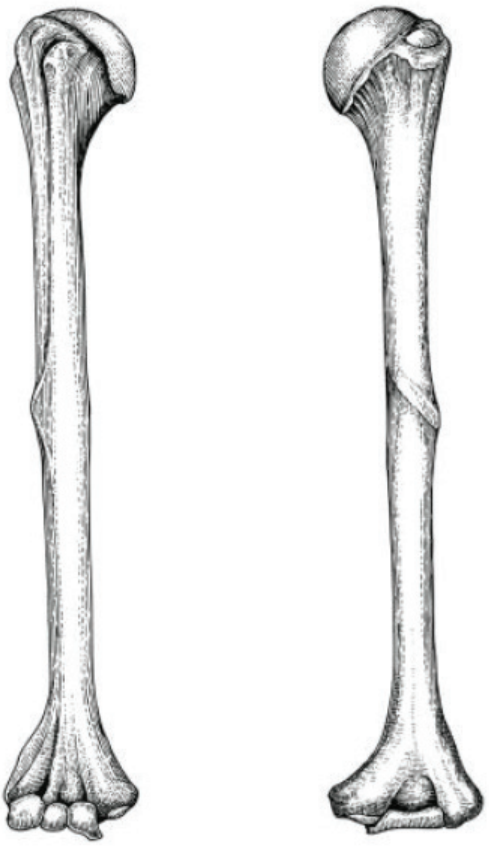
Chapter 24

ANATOMY OF THE HUMERUS, HUMERUS AND FOREARM FRACTURES

Mahmut ÇAY[1],
Sinan BAKIRCI[2]

1 Uşak University, Faculty of Medicine, Department of Anatomy, Uşak, Türkiye
2 İzmir Katip Çelebi University, Faculty of Medicine, Department of Anatomy, İzmir, Türkiye

The humerus is the longest and thickest bone of the upper limb. It is examined in three parts as extremitas proximalis, extremitas distalis and corpus humeri.



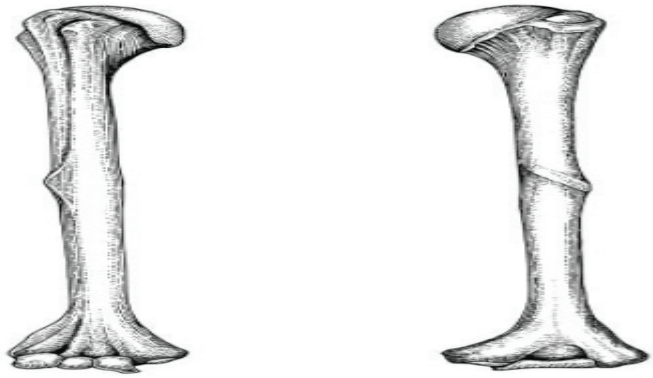
Humerus Ön Yüz *Humerus Arka Yüz*

Extremitas proximalis (Upper End)

In the proximal part, the caput humeri, which is the head of the humerus, is located medially. There is an angle of about 130 degrees between the caput humeri and the corpus humeri. Caput humeri joins the structure of the shoulder joint by articulating with the cavitas glenoidalis of the scapula. Below the caput humeri is the collum anatomicum, which is the anatomical neck. There are two bumps on the lateral of the upper end.

The larger of these raised bumps is called tuberculum majus and the smaller one is called tuberculum minus. Tubercles give downward crista-shaped extensions. These extensions are named crista tuberculi majoris and crista tuberculi minoris. Three muscles terminate on the tuberculum majus. These are the tendons of the supraspinatus muscle, the infraspinatus muscle,

and the teres minor muscle. In the tuberculum minus, the subscapularis muscle ends. Also; pectoralis major muscle ends in crista tuberculi majoris, while teres major muscle ends in crista tuberculi minoris. Between the two tubercles there is a groove called sulcus intertubercularis. The tendon of the long head of the biceps muscle passes through this groove. Latissimus dorsi muscle ends at the bottom of this groove. Numerous muscle terminations at the upper end of the humerus are of particular importance for movement. At the upper end of the humerus, there is the second neck between the head and the body. This surgical neck, called collum chirurgicum, is one of the most common humeral fractures.



Muscles ending in the proximal part of the humerus;

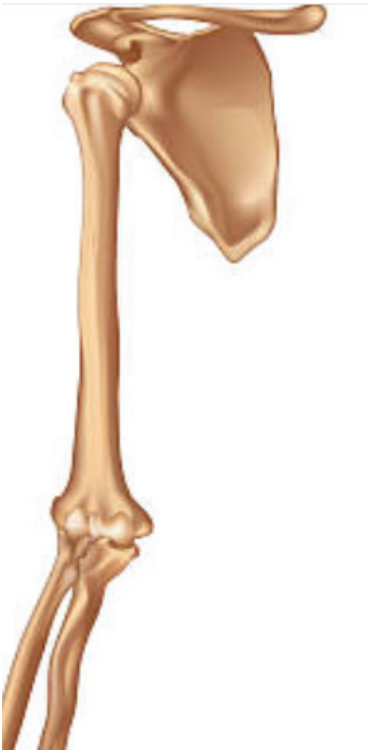
- Musculus subscapularis – Lesser tubercle (Tuberculum minus)
- Musculus supraspinatus – Greater tubercle (Tuberculum majus)
- Musculus infraspinatus – Greater tubercle (Tuberculum majus)
- Musculus teres minor – Greater tubercle (Tuberculum majus)
- Musculus teres major – Crest of lesser tubercle. Crista tuberculi minoris
- Musculus pectoralis major – Crest of greater tubercle. Crista tuberculi majoris
- Musculus latissimus dorsi – Intertubercular groove (Sulcus intertubercularis)

Corpus humeri

The body part of the humerus is called the corpus humeri. While the upper part of the body has a cylindrical structure, the lower side has a three-sided and thrihedral structure. In the upper part of the trunk there is a large rough area on the anterior-lateral side. The deltoid muscle ends in this rough area called tuberositas deltoidea. There is a groove at the bottom of tuberositas deltoidea, the depth of which varies according to the person.

In this groove called sulcus nervi radialis, profunda brachii artery (branch of brachial artery) is located together with the radial nerve. Sulcus nervi radialis runs downward from the posterior part of the humerus.

In the lower part of the trunk, the outer and inner sides, margo lateralis and margo medialis are seen. Margo lateralis continues downwardly crista supraepicondylaris lateralis and merges with epicondylus lateralis. Margo medialis, on the other hand, also extends as crista supraepicondylaris medialis and merges with epicondylus medialis. The lower side of the trunk that goes through the midline is called the margo anterior. There are two faces on the medial and lateral sides of this edge. There is facies anteromedialis in the medial and facies anterolateralis in the lateral. The face of the humerus, which is prominent in the lower posterior, is called facies posterior. While the corocobrachial muscle ends in the humeral body, the brachial muscle starts from the trunk.



Extremitas distalis (Lower End)

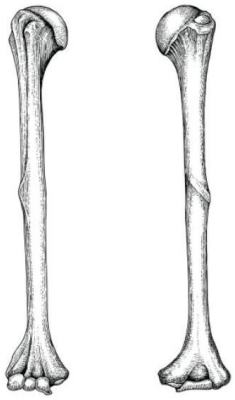
At the lower end, along with the condylus humeri, there are projections called epicondylus medialis and epicondylus lateralis on the medial and lateral sides. The “trochlea humeri” is seen in the form of a reel on the medial side of the condylus humeri. Trochlea humeri articulates with the incisura trochlearis in the ulna. On the lateral side, the capitulum humeri

is located and forms a joint with the head of the radius. Median nerve and brachial artery passage is seen from the lower end anterior midline.

On the anterior side of the lower end, on the upper side of the trochlea humeri, there is a pit named fossa coronoidea and during the flexion of the forearm, the protrusion of the ulna called processus coronoideus enters this depression. Fossa radialis is located on the upper part of the capitulum humeri and the head of the radius comes to this depression in forearm flexion. On the back of the lower end is the fossa olecrani, which is a large depression. At the extension of the forearm, the olecranon of the ulna enters the fossa olecrani.

At the lower end, there is a groove called sulcus nervi ulnaris between epicondylus medialis and trochlea humeri. The ulnar nerve passes through this groove. Sulcus nervi ulnaris is seen more clearly from the posterior.

In the distal part of the humerus, it forms the humeroradial joint with the radius, and the humeroulnar joint with the ulna. In addition, at the distal end of the humerus, together with the radius and ulna, it forms the articulatio cubuti known as the elbow joint.



Humerus Fractures

Surgical Neck Fracture of the Humerus

In the part of the humerus called as surgical neck; axillar nerve, posterior circumflex humeral artery and anterior circumflex humeral artery are important nerve and vascular structures. In fractures occurring in this region, the structures damaged in general are seen as axillary nerve and posterior circumflex humeral artery.

Fracture of the Body (Shaft) of the Humerus

There are two important structures damaged in humeral body fractures. The radial nerve in the sulcus nervi radialis and the profunda brachii artery are two important formations that are damaged in shaft fractures.

Distal Fracture of the Humerus

The structures that are generally damaged in distal fractures become median nerve and brachial nerve. If the fracture occurs on the epicondylus medialis side, the ulnar artery passing through it is very likely to be damaged.

Forearm Fractures

Monteggia fracture: It is the coexistence of the fracture of the ulna body and the radial head dislocation caused by the rupture of the ligamentum annulare radii.

Galeazzis fracture: The fracture of the proximal 1/3 of the radius is accompanied by dislocation of the distal end of the ulna.

Colles fracture: It is a fracture of the distal end of the radius seen in falls on the palmar surface of the hand while the hand is in extension. Since the fracture image resembles a food fork, it is sometimes referred to as “food fork deformity”. It is more common in people over the age of 50.

Smith fracture: In contrast to Colles fracture, the distal radius fracture occurs as a result of falling on the dorsal side of the hand.

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Chapter 25

NECK TRIANGLE AREAS AND ITS CLINICAL IMPORTANCE

Mahmut ÇAY[1],
Sinan BAKIRCI[2]

1 1.Uşak University, Faculty of Medicine, Department of Anatomy, Uşak, Türkiye

2 2.İzmir Katip Çelebi University, Faculty of Medicine, Department of Anatomy, İzmir, Türkiye

NECK ROOT

The area between the front of the cervical vertebra and the upper part of the apertura thoracis superior is called the neck root.

Structures in the root of the neck

Prevertebral muscles

Lateral vertebral muscles

Cervical plexus

Subclavian artery

Subclavian vein

Sympathetic trunks

Deep cervical lymph nodes

Thoracic duct

Trachea

Oesophagus

Thyroid gland

Parathyroid gland

Prevertebral Muscles (In Front Of The Cervical Vertebrae)

It is located in the groove between the cervical vertebrae and the bodies of the first three thoracic vertebrae and their transverse protrusions.

- Rectus capitis lateralis muscle
- Rectus capitis anterior muscle
- Longus capitis muscle
- Longus colli muscle

When these muscles contract unilaterally, they bend the head and neck to their sides (lateral flexion). When they contract bilaterally, they bend the head and neck forward (head flexion). Their innervations come from the anterior branches of the cervical spinal nerves.

Muscles on the outside of the cervical vertebrae

There are three muscles on the side, deep, right and left of the neck. These are called scalene muscles. These muscles extend between the transverse projections of the cervical vertebrae and the 1st and 2nd ribs.

- Anterior scalene muscle
- Middle scalene muscle
- Posterior scalene muscle

When the upper ends of the muscles are fixed, they help inspiration by lifting the ribs up. When the lower ends are fixed, they bend the neck and indirectly the head to their side. If the muscles of both sides work together, they stabilize the neck and head. It is innervated by the anterior branches of the cervical spinal nerves.

MUSCLES THAT MOVE THE HYOID BONE

The hyoid bone is connected with the surrounding organs (pharynx, larynx, tongue) with the help of various ligaments and muscles. Therefore, the hyoid bone moves during speech and swallowing movements. The muscles adhering to the hyoid bone are eight in total and are examined in two parts as the suprahyoid and infrahyoid muscles.

A) Suprahyoid muscles

1) Digastric muscle: It has two 'bellies. The anterior belly starts from the digastric fossa. Its posterior belly is larger and starts from the mastoid process. Both bellies extend towards the hyoid bone and join a common tendon. This tendon pierces the stylohyoid muscle and attaches to the body of the hyoid bone.

The anterior belly helps open the mouth by pulling down the mandible. The posterior belly raises the hyoid bone upwards. The anterior belly is innervated from the mandibular nerve and the posterior belly from the facial nerve.

2) Stylohyoid muscle: Starts at the styloid process. It ends in the hyoid bone and pulls the hyoid bone up. It is innervated by the facial nerve.

3) ***Mylohyoid muscle***: It forms the floor of the mouth by closing the opening between the arms of the mandible. It starts from the mylohyoid line. It ends in the hyoid bone and mylohyoid raphe. Mylohyoid raphe is a connective tissue that extends from the tip of the jaw to the hyoid bone. It plays a role in chewing, swallowing, sucking and speaking. Raises the hyoid bone and floor of the mouth. Its tongue rests on the palate. It is innervated by the mandibular nerve.

4) ***Geniohyoid muscle*****:** It starts from the spina mentalis and ends at that hyoid bone. It lifts the hyoid bone up and forward. In this way, the mouth of the larynx moves away from the pharynx during swallowing. It is innervated by the first spinal nerve.

B) Infrahyoid muscles

1) ***Sternohyoid muscle*****:** starts from the inner end of the clavicula and the manubrium sterni. It ends in the body of the hyoid bone. It pulls down the hyoid bone. Its nerve comes from the ansa cervicalis.

2) ***Sternothyroid muscle*****:** It starts from the manubrium sterni and the first cartilage rib. It terminates in the thyroid cartilage and pulls the thyroid cartilage down. Its nerve comes from the ansa cervicalis.

3) *Thyrohyoid muscle*: It starts from the thyroid cartilage. It ends in the great horn of the hyoid bone. If the thyroid cartilage is fixed, it pulls down the hyoid bone. If the hyoid bone is fixed, it pulls the thyroid cartilage up. Its nerve comes from the first cervical spinal nerve through the hypoglossal nerve.

4) *Omohyoid muscle*: It is a muscle with two bellies. The superior belly part starts from the middle beam, the inferior belly part starts from the incisura scapulae. The superior belly ends in the hyoid bone. The inferior belly ends in the middle beam. It pulls down the hyoid bone. Its nerve comes from the cervicalis.

NECK REGIONES (REGIONES CERVICALES)

Except for the nape region, each half of the neck is divided into two main topographic regions anterior and posterior by the sternocleidomastoid muscle (SCM). The anterior region is called regio cervicalis anterior, and the posterior region is called regio cervicalis lateralis. The area covered by SCM is examined as a separate region (regio sternocleidomastoidea).

In the superficial topography of the neck, there are also smaller subregions in the deep and subfacial planes. These subregions, which are generally triangular, are called "neck triangles". These triangles have great clinical and surgical significance; however, it is difficult to determine superficially. Neck triangles can be shown precisely during surgery or dissection.

Skin and subcutaneous layer: The skin covering the area is thin, mobile and stretched. There is a small amount of adipose tissue and platysma in the subcutaneous layer. Immediately deep in the platysma are the external jugular vein and the superficial branches of the cervical plexus. These nerves are distributed from the punctum nervosum to the neck. This nerves;

1. Great auricular nerve
2. Minor occipital nerve
3. Transverse cervical nerve
4. Supraclavicular nerves

Sometimes the anterior jugular vein crosses the lower part of the region by passing through the surface of the SCM.

STERNOCLEIDOMASTOID REGION

The boundaries of this region conform to the boundaries of SCM on the surface. The area shows a distinct swelling due to the muscle mass. The hollow area between the two heads of the muscle, caput sternale and caput

claviculare, is called fossa supraclavicularis minor. Below the SCM is the neck vascular-nerve package. In this respect, it has clinical significance. Structures crossing the vasculer-nerve package from the anterior side; digastric muscle, stylohyoid muscle, omohyoid muscle and hypoglossal nerve. There are deep lateral cervical lymph nodes adjacent to the packet.

Vascular-nerve package of the neck: Deep in the sternocleiudomastoid muscle, the vagina carotica and the structures contained within it are called the neck vascular-nerve package. Fine fibers that separate from the carotid sheath divide this space into three separate channels. The inner one of these ducts belongs to the common carotid artery, the outer one to the internal jugular vein, and the middle one to the vagal nerve.

ANTERIOR CERVICAL REGION (REGIO CERVICALIS ANTERIOR)

The limits; It forms anterior median line in front, corpus mandible at the top and SCM on the outside. Regio cervicalis anterior; divided into four lower triangles: trigonum submentale, trigonum submandibulare, trigonum caroticum and trigonum musculare.

Submental triangle: It is the area between the venter anterior of the digastric muscle on the outside, the body of the hyoid bone below, and the anterior median line inside. The mylohyoid muscle makes the floor of the region. Inside the triangle are loose connective tissue and adipose tissue and 2-3 lymph nodes (submental lymphatic nodes).

Submandibular triangle: The lower edge of the corpus mandibulae makes the upper border, the anterior and posterior borders the venter anterior and venter posterior of the digastric muscle. At its base is the mylohyoid muscle and hyoglossal muscle.

Structures in the submandibular triangle;

- Submandibular gland
- Facial vein
- Submandibular lymphatic nodes
- Hypoglossal nerve

Those in the deeper plan of the submandibular triangle;

- Lingual nerve
- Glossopharyngeal nerve

Carotid triangle: It is the most clinically important triangle of the neck, and it is the triangle where the “neck vasculer-nerve package” partially emerges from the protection of the SCM and becomes superficial. The structures that form the borders of the triangle; The anterior edge of the

SCM muscle is the superior belly of the omohyoid muscle, the stylohyoid muscle and the posterior belly of the digastric muscle.

The structures in this triangle;

- Last part of common carotid artery
- Beginnings of external carotid artery and internal carotid artery
- Initial sections of many branches of the external carotid artery
- Glomus caroticum (Carotid body)
- Internal jugular vein
- Vagal nerve
- Hypoglossal nerve
- Superior laryngeal vein
- Various lymph nodes

Muscular (omotracheal) triangle: Omohyoid muscle on the upper outer side, the anterior edge of the SCM muscle on the lower outer side and the anterior median line on the inner side in the middle. There are infrahyoid muscles within the muscular triangle. When the right and left two muscular triangles are evaluated together, the visceral region of the neck (Regio laryngeotrachealis) is revealed. In this region; The presence of thyroid gland, larynx, parothyroid glands, trachea, laryngopharynx and oesophagus increases the importance of the triangle in terms of surgery.

LATERAL CERVICAL REGION (REGIO CERVICALIS LATERALIS)

The borders of the region; Anteriorly, it is bounded by the posterior edge of the SCM muscle, posteriorly by the anterior edge of the trapezius muscle, and from below by the upper edge of the clavicula. The triangle within these boundaries is called trigonum cervicale posterior or trigonum colli laterale.

Regio cervicalis lateralis is divided into two unequal parts with the infrerior belly of the omohyoid muscle. Above is trigonum occipitale, below is trigonum supraclaviculare (omoclaviculare).

Omoclavicular triangle (supraclavicular triangle): The structures that form the borders of the triangle are the upper edge of the clavicula, the venter inferior of the omohyoid muscle, and the posterior edge of the sternocleidomastoid muscle.

Structures in the subcutaneous tissue in the omoclavicular triangle;

- External jugular vein
- Supraclavicular nerves

Deep structures in the omoclavicular triangle;

- Subclavian vein and some branches
- Supraclavicular part of the brachial plexus

Occipital triangle: It is the widest triangle of the lateral neck region. Anteriorly, the posterior edge of the SCM muscle borders the venter inferior of the omohyoid muscle below and the trapezius muscle behind.

Structures located in the deep (subfacial position) of the occipital triangle;

- Accessory nerve
- Supraclavicular nerves
- Transverse cervical artery and vein
- Suprascapular artery
- Suprascapular nerve

THE BACK OF THE NECK (NAPE) AREA = REGIO CERVICALIS POSTERIOR

Below, the biacromial line passing through the processus spinosus of the cervical seventh vertebra in the middle, the horizontal line passing through the protuberantia occipitalis externa (inion) above, and the outer edges of the pars descendens parts of the right-left trapezius muscle on the sides. The upper part of the region has a thick skin, with scalp characteristics. Subcutaneous tissue consists of fat and connective tissue.

The buildings from inside to outside;

- Third occipital nerve (the least occipital nerve)
- Greater occipital nerve
- Lesser occipital nerve
- Branches belonging to the great auricular nerve

The most superficial muscle of the region is the trapezius muscle. Structures located deep from the surface by lifting the trapezius muscle;

- Splenius capitis muscle
- Semispinalis capitis muscle
- Longissimus capitis muscle
- Greater occipital nerve (back of C2) pierce the semispinalis capitis muscle; Near it are branches of the occipital artery.

CLINICAL IMPORTANCE OF THE REGION

Platysma Paralysis (Platysma paralysis)

Platysma palsy, which results in injuries involving the cervical branch of the facial nerve, causes the skin to sag from the neck. Therefore, in surgical dissection of the neck, a little more attention is required to protect the cervical branch of the facial nerve.

Congenital Torticollis

Torticollis, caused by fibrous tissue tumors that develop from the SCM muscle before birth, is the most common type. This lesion causes the head to turn to one side and the non-defective side of the face. During birth, attention should be paid to the baby's head. In occasional difficult births, as a result of the child's head being pulled, the fibers of the SCM muscle can be torn off and injured. As a result of this event, part of the SCM muscle may become numb. If not treated, this lesion may result in torticollis. Flexion deformity is seen in the neck.

Spasmotic Torticollis

It is commonly known as cervical tonus disorder or curved neck. It usually starts between the ages of 20-60. It is especially seen with spasm of lateral neck muscles such as SCM muscle and trapezius muscle. Characteristics; turning, bending, or staying in flexion or extension of the neck. It is seen that the neck turns outward and forward involuntarily.

Cutting the external jugular vein

If it is cut along the posterior edge of the SCM muscle where it pierces the ceiling of the posterior cervical triangle, the lumen of the vein opens into the superficial layer of the fascia cervicalis profunda and negative air pressure is sucked into the vein. This situation causes cyanosis in the form of bruising on the skin and mucous membranes as a result of the decrease in the concentration of hemoglobin in the blood. Meanwhile, the resulting venous air embolism fills the right half of the heart in the form of foam. As a result, blood flow almost stops. This leads to difficulty breathing (dyspnea). Applying pressure to the ruptured external jugular vein prevents air entry into the blood until the vessel is sutured.

Increased prominence of the external jugular vein in the neck.

The external jugular vein serves as an "internal barometer". When venous pressure is high (heart failure) it becomes evident throughout the entire neck. Therefore, routine evaluation of the external jugular vein on physical examination provides important clues in the diagnosis of heart failure, superior vena cava obstruction, enlarged supraclavicular lymph nodes, and increased intra-thoracic pressure.

Severing of the phrenic nerve

In phrenic nerve damage, there is paralysis in the half of the diaphragm where the nerve is dispersed. Unilateral short-term diaphragm paralysis occurs in phrenic nerve block.

Nerve block in the posterior cervical triangle

Before surgery, the nerve block to be made to the nerves in the cervicales plexus and brachial plexus for regional anesthesia is prevented from the transmission of nerve impulses. In cervical plexus anesthesia, anesthetic substance is applied from various points along the posterior edge of the SCM muscle. The basic point is where the upper and middle 1/3 of the muscle meet.

Surgical dissection in the carotid triangle

Carotid triangle; It is an important localization for the commun carotid artery and its branches, cervical part of the sympathetic trunk, vagal nerve, hypoglossal nerve and internal jugular vein. During surgical operations in the carotid triangle, hoarseness may occur as a result of compression of the vagal or reccurent laryngeal nerve or damage to these nerves.

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Chapter 26

GASTROESOPHAGEAL REFLUX DISEASE[1]

Şeyma TRABZON[2],
Havva SERT[3]

1 *Şeyma Trabzon'un yüksek lisans tezinden üretilmiştir.*
2 *Sakarya Üniversitesi, Sağlık Hizmetleri MYO, Tıbbi Hizmetler ve Teknikleri Bölümü, İlk ve Acil Yardım Programı.*
3 *Sakarya Üniversitesi, Sağlık Bilimleri Fakültesi, İç Hastalıkları Hemşireliği Anabilim Dalı*

In the guideline published by the American College of Gastroenterology (ACG), gastroesophageal reflux disease is defined as "*the symptoms or complications originating from the reflux of gastric substance to esophagus or upper locations, to oral cavity (including larynx) or to lungs.*" (Katz, Gerson, & Vela, 2013). Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal system disease that occurs as a result of the entrance of gastric acid to the esophagus (Cătinean, Neag, Pop 2017). GERD is a chronic and frequently seen disease (Yamasaki, Hemond, Eisa, Ganocy, & Fass, 2018). It is important to reach a consensus for the symptoms of GERD. The organs affected by the reflux of gastric substances are the oral cavity, esophagus, and lungs. GERD can be classified as the existence of symptoms without erosion in the endoscopic examination (non-erosive disease) or erosions can be detected with GERD symptoms (Katz et al., 2013). Gastroesophageal reflux disease also has negative effects on larynx and pharynx. This condition emerged the definitions of laryngopharyngeal reflux (LPR) (LFR) or supraesophageal reflux (SERD). Extraesophageal reflux definition has also been started to be used with the acknowledgment of the relationship between certain asthma and chronic cough symptoms with the reflux of gastric acid to the esophagus. GERD includes symptoms and findings of the esophagus, larynx, pharynx, and respiratory tracts (Civriz ve Palabıyıkoğlu 2009). The most significant symptom is retrosternal burning. It is rarely a cause of death, however, it causes significant morbidity due to its complications (Yılmaz ve Soykan 2004).

Physiological reflux attacks usually take place after eating, they have short durations, asymptomatic and are not observed at nights. Pathological reflux, on the other hand, causes mucosal damage and inflammatory changes and symptoms are usually observed in patients (Stoller, Michota, Mandell 2014).

1. Physiopathology of Gastroesophageal Reflux Disease

Although there are many factors that are effective in the emergence of the disease, the most basic reason for the emergence of GERD is the dysfunction in the anti-reflux barrier that prevents excessive amounts of reflux and the dysfunction in the mechanisms that provide the fast purification of esophagus from the gastric substance (Menezes and Herbella 2017; Chen and Brady 2019). The defense factors that protect the esophagus are classified into three as anti-reflux barrier, luminal purification, and tissue resistance.

The anti-reflux barrier protects the esophagus by decreasing both the frequency of reflux attacks and the volume of substance that refluxes to the esophagus. The most important elements of the anti-reflux barrier are the lower esophagus sphincter and the crural part of the diaphragm. Lower esophagus sphincter (LES) consists of a circular muscle layer of 1-3.5 cm. It

prevents the gastric substance to enter the esophagus by creating a pressure that is more than the pressure in the stomach. The muscles that constitute LES are different from the muscles in the esophagus body and they stretch spontaneously. The dysfunctions of LES are; intrinsic weakness of lower esophagus sphincter, inadequate LES respond against the increased abdominal pressure and spontaneous free reflux. Reflux attacks usually take place during the temporary relaxation of the lower esophagus sphincter. The temporary relaxation of the lower esophagus sphincter occurs without a pharyngeal stimulus and it is independent of the peristaltic movements of the esophagus. It takes longer than the LES relaxation that occurs due to swallowing. When the LES relaxation pressure is zero or near to zero, it can't sufficiently resist the reflux and spontaneous free reflux occurs. LES pressure quickly increases in the case of coughing or straining in which abdominal pressure suddenly increases and the reflux attack is prevented. If the LES pressure does not increase as much as the increase of sudden abdominal pressure increases, reflux is observed (Yılmaz ve Soykan 2004; Lee and Mccoll 2013; Chen and Brady 2019).

Temporary relaxations of lower esophagus sphincter are the most important reflux mechanisms in Gastroesophageal Reflux Disease. Primary peristaltic movement occurs as a result of swallowing and it relaxes the LES. The relaxed LES remains open for 3-10 seconds for the bite to enter the stomach. Temporary relaxations of lower esophagus sphincter are observed independently from swallowing and without peristaltic movement. Temporary relaxations of lower esophagus sphincter that occur as a result of the straining of stomach fundus are a ventilation mechanism that provides the gas in the stomach to be released. Agents such as atropine, morphine, and serotonin inhibit the temporary relaxations of the lower esophagus sphincter. While LES relaxations are observed two to six times in healthy individuals, it is observed three to eight times in individuals with GERD (Yılmaz ve Soykan 2004; Herbella et al. 2018).

One of the formations that damage the anatomical structure of the gastroesophageal junction is hiatus hernia. In hiatus hernia, diaphragmatic sphincter functions degenerate. The esophagus purification of these patients is impaired and temporary LES frequency is increased.

The esophagus passes through the esophageal hiatus which is located in the right crural of the diaphragm. When the crural part of the diaphragm strains, the crurals come together and encircles the distal esophagus. Encircling the lower end of the esophagus by the crurals like a clamp when the intra-abdominal pressure increases and during the inspiration provides a barrier that prevents reflux (Lee & Mccoll, 2013; Menezes & Herbella, 2017).

In addition to the crural diaphragm and lower esophagus sphincter, other anatomic formations in the distal esophagus also operate as an anti-reflux barrier. The acute angle (Cardiac notch) that emerges with the merging of the stomach and esophagus and the inclusion of a part of the distal esophagus in the abdomen are examples of this anti-reflux barrier (Tack and Pandolfino 2018).

Luminal Purification; the potentially hazardous material in this area should be purified quickly so that there won't be any damage in the esophageal mucosa. These materials that reflux from the stomach is removed by four mechanisms. These are; gravity effect, peristaltic activity, saliva, and esophageal bicarbonate secretion. Gastroesophageal reflux disease may occur when the purification of esophagus lumen dysfunctions. The emergence of reflux as a result of the inadequate peristaltic movements in patients diagnosed with scleroderma, reflux attacks during sleep due to the decrease of gravity effect, and insufficient saliva can be given as examples for the dysfunction f luminal purification (Yılmaz ve Soykan 2004; Civriz ve Palabıyıkoğlu 2009; Herregods, Bredenoord, Smout 2015).

Tissue Resistance; tissue resistance consists of mucosal structures. These structures are classified as pre-epithelial, epithelial, and post-epithelial defense factors according to the anatomic vicinity of epithelial that constitute the esophagus mucosa. The pre-epithelial defense factors in the esophagus are the mucosa layer, motionless water layer, and superficial bicarbonate ions. The esophagus is weaker when compared to the stomach and duodenum. Epithelial defense factors also contain physical and functional formations. These formations prevent the hydrogen ions to enter the cell and between the cells. Post-epithelial defense factors are provided by the bloodstream. While the bloodstream removes carbon dioxide and hydrogen ions from the area, it provides protection by carrying foodstuffs, oxygen, and bicarbonate. Cell renewal is quite slow in the esophagus and for this reason, it does not have a strong effect in defense. The reason why individuals whose esophageal purification is normal and who have a strong anti-reflux barrier experience reflux esophagitis is that their epithelial resistance is inadequate. Alcohol, smoking, non-steroid anti-inflammatory drugs, and hypertonic solutions cause the epithelial resistance to become dysfunctional (Yılmaz ve Soykan 2004; Civriz ve Palabıyıkoğlu 2009).

Other significant factors for the emergence of reflux are the slowing of gastric emptying, the nature, and the volume of gastric content. The delay in gastric emptying facilitates reflux by increasing the stomach volume and accelerating the relaxation of lower LES and increasing the gastroesophageal pressure difference. While the role of acid in the gastric content is important in GERD, its common movement with pepsin constitutes the basic mechanism of mucosal damage. Oversecretion of the

acid may accompany high esophagitis prevalence (Stacher et al. 2000; Dobrucalı 2007; Stoller et al. 2014; Wang et al. 2019).

2. Epidemiology in Gastroesophageal Reflux Disease

While the frequency and severity of gastroesophageal reflux symptoms differ from society to society, it is commonly seen all around the world (Dent, El-Serag, Wallander, Johanson 2005).

2.1. Gastroesophageal Reflux Disease in the World

The incidence of GERD increases each year with the change in nutrition style and lifestyle that became faster with the developments in the economy (Chen, Xiong, Zeng, Wei, Tan 2018). Epidemiological studies were conducted on the prevalence of this disease based on regurgitation and heartburn which are the most frequently observed symptoms of GERD. In a study, it was determined that while GERD prevalence was 10-20% in western countries, Asia prevalence was lower (Katz et al., 2013). In the systematic compilation performed by El-Serag et al., it was reported that the prevalence of GERD with heartburn and regurgitation once a week was 18.1-27.8% in North America, 23% in South America, 11.6% in Australia, and 25.9% in Europe (El-Serag HB, Sweet S, Winchester CC, 2014). In a study conducted in Italy with 1033 participants, 458 individuals (44.3%) stated that they have reflux symptoms and 245 of this population (23.7%) experienced these symptoms more than two times a week (Zagari et al., 2008). In another study conducted in Israel, the prevalence of reflux symptoms once a week was 12.5% (Moshkowitz, Horowitz, Halpern, Santo 2011).

2.2. Gastroesophageal Reflux Disease in the World

In a study conducted in 17 provinces of Turkey with 3214 participants, GERD prevalence was determined as 22.8% and GERD was determined at the rate of 18.9% in males and 26.2% in females. In the same study, it was also determined that GERD prevalence was higher in the northern part of our country (Bor, Kitapçıoğlu, Kasap 2017). In a cross-sectional study conducted in 20 provinces of Turkey with 8143 participants, it was determined that GERD was more prevalent in females (Mungan, 2012). In the same study, 815 individuals (10%) who stated that they have pyrosis symptoms in the last week and 1089 individuals (13.4%) who stated that they have regurgitation symptoms were determined (Mungan, 2012). In another study conducted in our country with 1188 participants, GERD prevalence was determined as 10.9%. The relationship between the age and body mass index with GERD was also determined and it was observed that the reflux prevalence was similar to western countries (Çakır ve ark 2018). In another prevalence study conducted in the Central Anatolian region in Turkey with 1345 participants, the GERD prevalence ratio was determined as 19.3% (Yönem ve ark 2013).

It was observed that in the epidemiological studies conducted on GERD, regurgitation was more prevalent. Turkey is located in the middle of east and west in world geography and it can be observed that GERD prevalence resembles both sides (Bor ve Yüksel 2017).

3. Clinical Picture in Gastroesophageal Reflux Disease

Clinical symptoms in gastroesophageal reflux disease are classified as typical and atypical. Typical symptoms are pyrosis, dysphagia, regurgitation, water brash, odynophagia, and globus sensation. Atypical symptoms are posterior laryngitis, asthma, coughing, non-coronary chest pain.

Pyrosis is described as the burning sensation behind the breast bone. It is the most commonly seen symptom of GERD. The burning sensation can be felt in epigastrium, neck, and throat (Yurdakul, 2004). It may occur after the consumption of certain food (fried food, leavened pastry, and spices), certain beverages (coffee, brewed alcohol drinks) or intense smoking. When the lower esophageal sphincter loosens, some of the patients may experience pyrosis after eating or lying back and leaning upside-down (Yılmaz, Soykan, Dağlı 2004).

Dysphagia; The most frequently observed dysphagia cause is peptic tightness. Dysphagia develops firstly against solid food and then against liquid food in patients who experience long periods of GERD. The slowing of the peristaltic movements of the esophagus develops due to edema of inflammation in the esophagus mucosa. The emergence of the peptic structure is a significant pathology. Dysphagia can be observed in the existence of ulcers due to reflux (Doğan, 2009; Yurdakul, 2004).

Regurgitation; it is the reflux of stomach or esophagus content without difficulty, nausea, and retching. Patients usually state that undigested, burning and sour food contents reflux to their throat and mouth. The actions that make regurgitation easier are leaning forward, belching, and movements that increase intraabdominal pressure. (Bredenoord, Weusten, Curvers, Timmer, & Smout, 2006)

Water Brash; it is the slightly salty liquid that suddenly refluxes to the mouth. Neutralization is provided with alkali saliva for the acidic gastric content by excreting plenty of saliva.

Odynophagia: it means painful swallowing. It is observed when deep lesions and ulcers emerge in the esophagus.

Globus Sensation; it is the sense of fullness in the throat like a lump apart from the swallowing function. (Yurdakul, 2004)

Clinically, Gastroesophageal reflux disease was divided into two in the Montreal consensus as esophageal and extraesophageal syndromes. Patients who have esophagus symptoms of GERD but do not have mucosal

lesion in endoscopy are named as symptomatic syndromes. Esophageal-damaged syndrome is the definition given to patients who have lesion in endoscopy. (Vakil, Zanten, Kahrilas, Dent, Jones 2006)

Gastroesophageal reflux disease may manifest itself with symptoms apart from the esophagus. These symptoms are; chest pain (chest pain that spreads to the left arm, chin, and neck and gives a feeling of tightness can be observed as well. The relaxation of this paint with anti-acids and emergence after eating distinguishes it from angina pectoris), pulmonary complaints (asthma, bronchitis, bronchiectasis, aspiration pneumonia, idiomatic pulmonary fibrosis), ear, nose, and, neck problems (aphonia, coughing, globus, pharyngitis, otitis laryngitis, sinusitis, vocal cord granuloma, subglottic stenosis, laryngeal carcinoma), dental erosion, and sleep apnea (Doğan 2006; Madanick 2014; Lee et al. 2017). Regurgitation or retrosternal burning findings are mild or absent in these patients (Stoller et al. 2014). The clinical picture may change for erosive reflux disease, non-erosive reflux disease, and Barrett esophagus. There are typical symptoms in erosive reflux and they are related to food. They give a positive response to treatment. In non-erosive reflux disease, the symptoms are as severe as the erosive reflux and its relation with food is not typical. In Barrett esophagus, erosions are observed in every patient and the symptoms are severe (Yılmaz et al., 2004).

4. Complications in Gastroesophageal Reflux Disease

Ulcer, stricture, bleeding, adenocarcinoma, vocal cord granuloma, larynx carcinoma, aspiration pneumonia, asthma bronchitis, and Barrett esophagus are the complications observed in GERD. Bleeding is observed after the formation of ulcers and usually emerges as occult bleeding (Yılmaz et al., 2004).

Barrett Esophagus is the most serious complication of GERD. It is the name given to the metaplasia mucosa of normal squamous cell epithelial that emerges after reflux and substitutes columnar epithelium. Intestinal metaplasia is determined with biopsy. Endoscopic monitoring is regularly performed for patients with Barrett esophagus in order to screen adenocarcinoma. Adenocarcinomas observed in the esophageal and esophagogastric junction and one of the complications of gastroesophageal reflux complications is characterized by poor prognosis (5-year survival rate 20%) and higher prevalence in males. It was also stated in several studies that GERD is related to certain extraesophageal carcinomas including head-neck and lung cancer (Shaheen and Ransohoff 2002; Taylor and Rubenstein 2010; Ness-jensen and Lagergren 2016).

5. Diagnosis and Treatment in Gastroesophageal Reflux Disease

Diagnosis: It is believed that gastroesophageal reflux disease can be treated completely with an attentive symptomatic assessment. Typical

GERD symptoms are heartburn and the reflux of gastric content to the esophagus. The existence of typical symptoms for two times a week or more determines the presumptive diagnosis of GERD. Tests such as therapeutic trial, symptom surveys, endoscopy, esophageal manometry, esophagus pH monitoring, barium esophagus passage graph, non-catheter pH monitoring (bravo capsule), and high definition and impedance manometer can be performed for diagnosis (Dobrucalı 2007; Patti 2016; Iga et al. 2016).

Therapeutic Trial; anti-acid drugs are given to patients with heartburn complaints and getting a positive response is regarded as the existence of reflux. This condition is named as Proton Pump Inhibitor (PPI) trial (Patti, 2016). There is no consensus on the type, dosage, duration or result assessment of PPI. PPI treatment is usually suggested for at least two weeks and when half of the symptoms show recovery the disease is regarded as positive. Although this method is easy and common, its susceptibility and specificity are low (Iga et al. 2016).

Symptom Surveys; These are the documents that define GERD patients and frequently used in research studies. Their use is limited in daily practice due to low susceptibility and specificity (Iga et al., 2016).

Endoscopy; endoscopy is used in the determination of GERD complications such as esophagitis, stricture, Barrett Esophagus, and adenocarcinoma. Endoscopy is suggested for dysphagia, odynophagia, bleeding, and weight loss, patients who possess indicators of GERD, and other significant upper gastrointestinal system diseases. Conventional endoscopy provides the diagnosis of changes in esophagus mucosa in patients with non-erosive reflux.

Esophageal Manometer; it is the method used for excluding dysmotility such as Achalasia. It is applied to patients who did not respond to PPI treatment and before the anti-reflux surgery (Hunt et al., 2017; Patti, 2016).

Esophagus pH Monitoring: ambulatory pH monitoring is regarded as the golden standard in GERD diagnosis. It provides the measurement of acid exposure and determination of the relationship between the symptoms and reflux. This test is used when the patient is not using drugs, H_2 blocking agents should be stopped to be used three days before and PPI should be stopped to be used seven days before. Apart from the pH, it is also used for the determination of the reflux type (acidic, weakly acidic, non-acidic). Intra-esophagus pH value is above five in healthy individuals (Türkyılmaz and Aydın, 2012).

Barium Esophagus Passage Graph; Although it is not useful in GERD diagnosis, it provides information about the anatomic structure such as the existence, dimension, type, and the existence of esophagus tightness of Hiatus hernia (Patti, 2016).

High Definition and Impedance Manometer; high definition esophagus manometer is better than the diagnostic performance of conventional manometer. It is a standardized and objective measurement system that provides the simultaneous monitoring of the contractility of the esophagus. It is used in the assessment of dysphagia after the anti-reflux surgery. When it is merged with an impedance study, it can be distinguished from rumination and regurgitation related to GERD and it determines the belching related to GERD (Iga et al. 2016).

Non-Catheter pH Monitoring (Bravo Capsule); the wireless system of esophagus pH measurement (Bravo Capsule) is well-tolerated by the patient when compared to pH equipment and probes. It is more sensitive in establishing the relationship of reflux attacks with symptoms and the determination of acid reflux. Its cost is not efficient, cannot determine non-acidic reflux, and causes chest pain (Iga et al. 2016).

Treatment: The treatment is shaped according to the severity of GERD symptoms. Treatment may include one or more of the lifestyle change, drugs, and surgical treatment (Smith, 2016).

Lifestyle Change and Organization of Diet; It was determined that the risk of reflux-related esophagus adenocarcinoma decreases as the fibrous food in the diet increases. Slow, frequent, and low volume eating are suggested. Raising the bedhead at nights and lying on the left side eases the symptoms. Eating three hours before sleeping or more would decrease the amount of reflux. Smoking would cause reflux attacks by triggering coughing and it is a risk factor for GERD symptoms. Alcohol increases the production of gastric acid, loosens the lower esophagus sphincter, and causes regurgitation. Clothes that tightly wraps abdomen press the esophagus lower sphincter and cause gastric content to reflux to the esophagus. Obesity is a risk factor for GERD and causes regurgitation by increasing intraabdominal pressure. It was determined that excessive physical activity is also a risk factor in the emergence of GERD. In a study, it was stated that performing abdominal respiration would decrease reflux symptoms by decreasing abdominal pressure and it was suggested to teach abdominal respiration exercises to GERD patients (Smith 2016; Dağlı ve Kalkan 2017; Eherer 2014). It can be suggested for GERD patients to consume fibrous food, to lie on their left while sleeping (In the study of Loots et al. (2013), there wasn't a relationship between the reflux attacks and lying on left and right) and to raise bedhead, to lose weight for overweight individuals, to decrease or to quit smoking, to avoid stress, to stop drinking alcohol and eating at least two hours before sleeping, to avoid eating fatty food, not to lie down after eating, not to eat too much or too quickly or not to take excessive liquid since these precautions decrease the symptoms of GER (Kaltenbach, Crockett, Gerson 2006; Dağlı ve Kalkan 2017; Kobayashi et al. 2017; Kroch and Madanick 2017;).

Drug Treatment; medical treatment is suggested and used for patients whose GERD symptoms still continue despite the lifestyle changes. Medical treatment includes anti-acids, sodium alginate, and potassium bicarbonate, histamine 2 receptor antagonists, proton pump inhibitors, sucralfate, and gastrointestinal prokinetics (Sandhu and Fass 2018).

Endoscopic Treatment; it is the process of giving radiofrequency energy to the esophagus and stomach junction in order to increase the tonus of lower esophagus sphincter and to decrease the number of temporarily relaxed areas. It cannot treat the anatomic defects and it is not indicated in GERD patients with active ulcer and stenosis. It has a perforation complication (Souza et al., 2018).

Surgical Treatment; patients whose symptoms were not treated by drug treatment, emergence of permanent reflux due to insufficient lower esophagus sphincter, patients who experience complication during PPI treatment, young patients who do not want to use drugs for the rest of their lives, patients whose GERD is significantly related to hiatus hernia, and morbid obesity patients who cannot lose weight with the lifestyle change are the candidates for anti-reflux surgery (Patti, 2016). Laparoscopic Nissen fundoplication is used as the golden standard in surgery with minimally invasive treatment. Fundoplication related to esophageal hiatus calibration; it is effective in the improvement of life quality, the removal of typical and atypical symptoms in most of the patients, and the treatment of the anti-reflux barrier in patients with GERD. This method restores the function of the lower esophagus sphincter, decreases the risk of acid and non-acid reflux, Barrett Esophagus, and adenocarcinoma, and regains the gastroesophageal junction anatomy in patients with hiatus hernia (Nicolau, Lobonaiu, Constantinou 2018).

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Chapter 27

PELVIC INJURIES

Sibel GÜÇLÜ UTLU[1]

1 Emergency Medicine Clinic of Erzurum Regional Training and Research Hospital

INTRODUCTION

The pelvis plays a role in balancing, supporting, protecting the body and producing blood. It transfers the weight of the trunk and upper extremities to the lower extremities. Pelvis traumas constitute 3% of all musculoskeletal injuries [1]. Pelvic injuries vary from simple injuries to life-threatening severe injuries.

Pelvis traumas are usually caused by high-energy traumas such as motor vehicle accidents and falls from heights [2]. Factors such as advanced age, having had a pelvic operation and smoking carry a higher risk in pelvic trauma.

It is often associated with multiple injuries. Neurovascular structures, pelvic and urogenital organ injuries can be injured with pelvic bone fractures. Mortality rates vary between 10-50% according to the size of the injury and 60% of the mortality is caused by pelvic hemorrhages [3]. Bleeding that requires angiography is more common in patients above 60 years of age with severe pelvic injury. Therefore, the incidence of mortality and morbidity is high after such traumas. While urogenital, rectal and neurological complications are seen in the acute phase, it may cause sexual dysfunction and chronic pain in the long term. In the first stage of treatment, the aim is to keep the patient alive and stabilize vital signs. Therefore, the first respond in the emergency service is of vital importance.

GENERAL DESCRIPTION

Epidemiology

Pelvic fractures account for 3 percent of all injuries [1,4]. The mortality rate of pelvic fractures is 5-16% [5]. Only 1% of trauma deaths result from pelvic fractures. If there is a pelvic fracture above the age of 65, the mortality rate also increases. And generally, we can say that the mortality risk increases if a trauma patient has a pelvic fracture. Mortality is 20% in patients over 65 years of age [6].

Hemodynamically unstable patients have high mortality [7]. Almost 45% of open fractures get mortal [4].

Risk factors for pelvic fractures include hysterectomy, low bone mass, smoking, advanced age and a tendency to fall [8].

Mechanisms

High-energy traumas such as motor vehicle accidents are often responsible for pelvic fractures [9]. Pelvis injuries caused by high-energy trauma are usually accompanied by other injuries such as bleeding, abdominal organ injuries (liver, spleen, intestine), genitourinary injury (bladder, urethra), vascular injuries and neurological deficits. The

mechanism of iliac artery bleeding in pelvic trauma is the compression of the vessels and impairment of vessel wall integrity. Thoracic aortic dissection and rupture occurs in 1-2 percent of the patients with pelvic fractures as a result of blunt trauma. In individuals with immature bone structure, avulsion fractures may occur with the sudden, strong contraction of a muscle.

ANATOMY

The pelvis plays a role in balancing, supporting, protecting the body and producing blood. It transfers the weight of the trunk and upper extremities to the lower extremities.

It consists of the sacrum, the coccyx, as well as the ilium, ischia, and pubis. The acetabulum consists of the ilium, ischium and pubis (figure 1). The strong ligaments that connect the sacrum and pelvic bones are responsible for the main stability of the pelvis. Additionally, the ligaments between the pubic ramus the iliolumbar and lumbosacral ligaments in the pelvic ring maintain stability. While single fractures in the pelvic ring are stable fractures and do not separate, double fractures in this ring are unstable fractures and may cause separations.

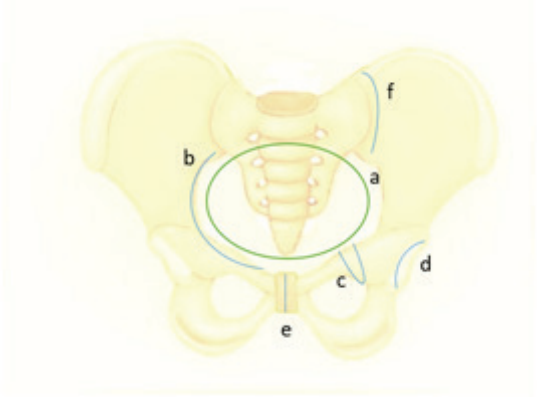


Figure 1. *a. Pelvic arcuate line, b. Iliopectineal line, c. Ilioischial line, d. Acetabular line, e. Symphysis pubis, f. Sacroiliac joint*

The arcuate line divides the pelvis into false (greater) / upward and downward / true (lesser) pelvis. In the arcuate line, there are the symphysis pubis in front, acetabulum and femur on both outer sides, and two sacroiliac joints at the back. The pelvis is rich in vessels and nerves. The iliac artery and venous vessels, branches of the lumbosacral plexus which is the thickest peripheral nerve of the body, and part of the genitourinary and gastrointestinal tract are also found in the pelvis.

In women; the urethra, uterus, ovaries and vaginais located in pelvis and in men; the prostate is located in the pelvis. All these structures require evaluation in pelvis injuries.

The pelvic artery system is the internal iliac artery and its branches. Usually, the internal iliac artery divides at the pelvic entrance area into the external iliac artery and the internal iliac artery. It is divided into parts as a posterior-anterior branch. The most important are the injuries to the obturator and internal pudendal arteries in pubic ramus fractures.

The pelvic venous system consists of veins parallel to the arterial system and the plexus in the anterior part of the sacrum. The sacral plexus is very susceptible to sacroiliac injuries and is a source of serious bleeding.

The neural network in the pelvis emerges from the nerve roots from L4 to S3, as the lumbosacral plexus. Damage to these nerves can cause bladder, bowel, and sexual dysfunction.

PREHOSPITAL MANAGEMENT

In pelvic trauma, the primary purpose of emergency healthcare services is to recognize the mechanism and to recognize possible injuries. Priority is the stabilization of the airway, respiration and circulation.

There is a possibility of pelvic fracture in patients with blunt trauma. Therefore, the injury mechanism of the patient should be questioned and transport to the hospital should be done properly. Before the hospital, the healthcare team who first saw the patient should question the patient's vital signs, localization and degree of pain, and the presence of additional pathologies. Unstable pelvic injuries, such as separation of the sacroiliac joints, cause severe retroperitoneal bleeding. Patients with hemodynamic instability are recommended to be stabilized by tying the pelvis even if there is no suspicion of pelvic trauma. For stabilization, pelvic ligation should be made at the level of great torachanters. Thus, pelvic volume is reduced, possible fracture fragments are stabilized and the risk of bleeding is reduced [10].

FRACTURE TYPES

Pelvic ring irregularity fractures, sacral, acetabular and avulsion fractures may occur.

Pelvic Ring Fractures

When the ring breaks, usually two fractures occur. Therefore, clinicians should closely examine the radiographs for additional injuries when a pelvic fracture is detected. Several classification schemes have been proposed for pelvic ring deteriorations. The most preferred of these is the Young and Burgess classification scheme. According to this classification, fracture types are categorized according to the injury mechanism and the direction of the force that causes the injury. In addition, according to the Young-Burgess classification, the need for transfusion of blood products increases in patients with major ligament injuries, that is, the possibility

of instability. In general, the available data indicate that a serious injury in the posterior part of the pelvic ring also increases the complication rates.

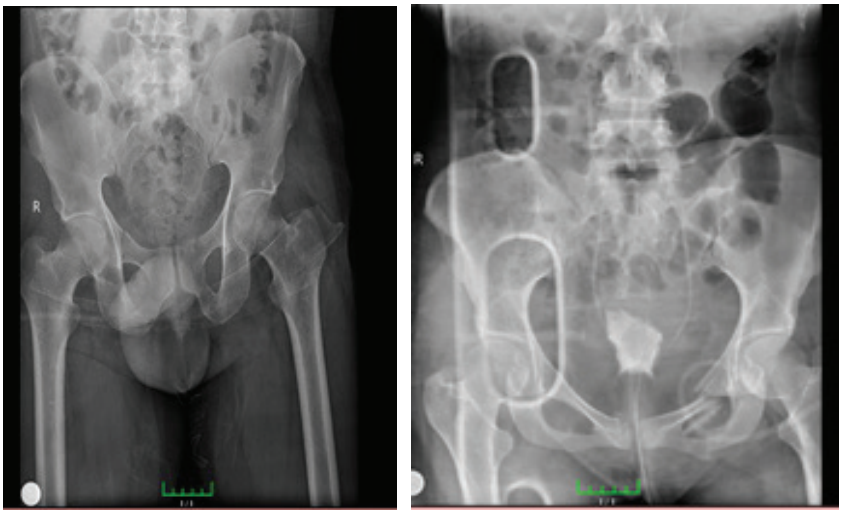
1- Lateral Compression Fractures (LC)

Almost half (50%) of injuries occur by this mechanism. It usually occurs when a motor vehicle hits a pedestrian from the side.

Type 1 - It is the most common type. With unilateral or bilateral ramus fractures, a sacral compression fracture occurs on the trauma side. Serious complications rarely occur.

Type 2 - Iliac bone fracture occurs on the trauma side.

Type 3 - Type 1 or 2 injury on the side of the trauma and an open book injury on the opposite side of the trauma. (also known as "wind-swept pelvis")



Radiography 1.a. and 1.b. *LC type 1*

2-Anteroposterior Fractures (APC)

It is the second most common mechanism (25%). It usually occurs when a motor vehicle hits the pedestrian from the front.

Type 1 - Symphysis pubis enlargement generally less than 2 cm and posterior pelvic ring ligaments intact.

Type 2 - Widening of the anterior sacroiliac joint due to disruption of the anterior parts of the sacroiliac, sacrotubereous and sacrospinous ligaments. It may be evidence of enlargement of the symphysis pubis and enlargement of the anterior pelvic ring in ramus fractures. The posterior part of the sacroiliac ligament remains intact.

Type 3 - Complete deterioration of the sacroiliac joint with anterior

pelvic ring injury like Type 2 (Radiography 2.a)

3-Vertical Shear Fractures (VS)

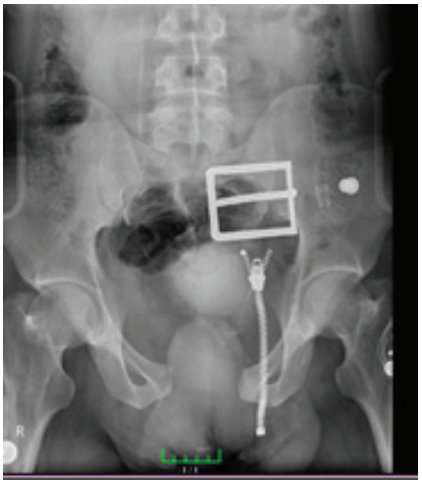
Due to a longitudinal force applied to the pelvis, the hemipelvis is displaced upwards or backwards. Anterior pelvic ring injuries can include enlargement of the symphysis pubis or unilateral or bilateral ramus fractures. Posterior pelvic ring injuries are generally seen in the sacroiliac joint, but may include iliac wing or sacrum fractures.

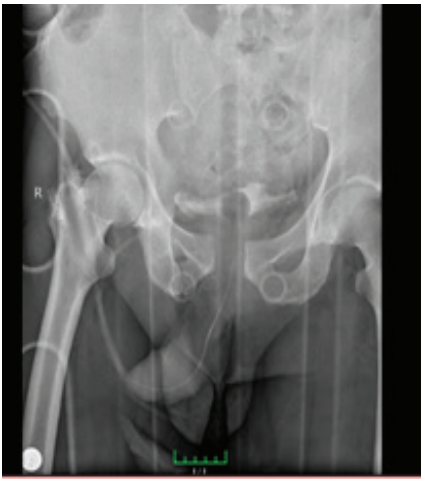
4-Combined Mechanism Fractures

It can be seen as combinations of other injury types (20%).

5-Open Book Fractures

This fracture includes posterior pelvic fracture or ligamentous injury and anterior injury. That is, according to the Young and Burgess classification, other types of pelvic fracture mechanisms can be defined as open book fractures depending on the degree of damage. Widening of the anterior pelvic ring more than 2.5 cm increases the risk of bleeding by causing injury to the posterior pelvis. (Radiography 2.b)





Radiography 2.a. *APC type 3, namely "open book fracture",* **Radiography 2.b.** *Open book fracture*

Sacral Fractures

Classification by neurological injury rate:

Region 1 - Lateral to the sacral foramen (5.9%, usually L5 root)

Region 2 - Via sacral foramen (28.4%, usually sciatica, rarely bladder or bowel involvement)

Region 3 - Medial to the sacral foramen in the central canal (≥%50, mostly bowel and bladder involvement or sexual dysfunction)

Acetabular Fractures

The acetabulum has anterior and posterior columns. The anterior column part is comprised of the anterior iliac wing, superior pubic ramus, and the anterior wall of the acetabulum. The posterior column is formed of the ischium, ischial tuberosity and the posterior wall of the acetabulum. Letournel and Judet's classification is used to identify acetabular fractures [11]. It is frequently accompanied by hip fracture-dislocation, knee joint and femur injury. Sciatica injury is often expected in acetabular fractures. Whether the fracture is dissociated or not leads the treatment. Orthopedic consultation should be applied immediately for all these accompanying injuries. Acetabular fractures are categorized as simple and complex fractures.

Simple Fractures

Posterior wall - the most common (23.3%). Accompanied by the dislocation of the femoral head towards the posterior part. (Radiography 3.a.)

Posterior column - Ilioischial fracture, in its presence may be femoral dislocation. Femoral dislocation tends to be medial

Anterior wall - fracture in the upper-anterior acetabulum

Anterior column - deterioration of the iliopectineal line, anterior femoral dislocation is common in its presence

Transverse - Separation in the acetabular joint surface

Complex Fractures

They are combinations of simple fractures.

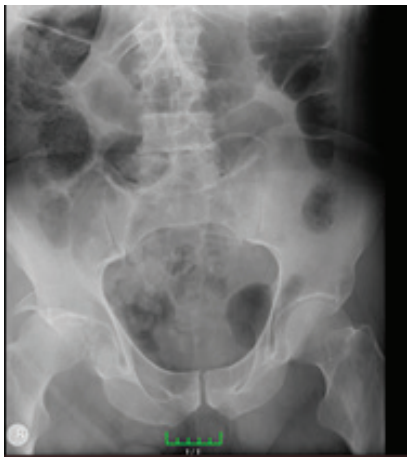
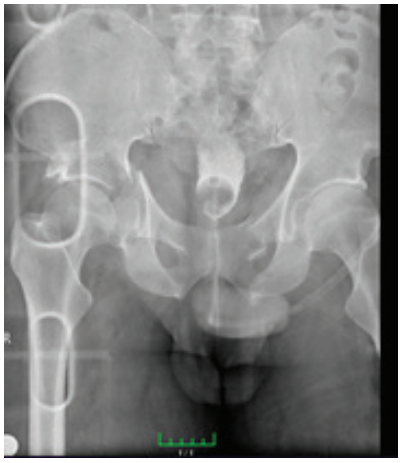
T-shaped - Combination of transverse fracture and vertical fracture

Posterior wall and posterior column - Posterior column and posterior wall are displaced significantly from each other; sciatic nerve damage often accompanies.(Radiography 3.b.)

Transverse and posterior wall - combination of these two wall fractures

Anterior column and posterior hemitransverse - Transverse posterior column fracture and anterior wall or column fracture

Both columns - The most complex acetabular fracture and the entire acetabulum is separated. Shaped like a floating acetabulum. The floating acetabulum part may stay with the femoral head.

Radiography 3.a. *Posterior wall (Simple Fractures),* **Radiography 3.b.** *Posterior wall and posterior column (Complex Fractures)*

Avulsion Fractures

It is frequently seen in athletes between the ages of 14-17. It occurs as a result of sudden and strong muscle contraction in high-energy trauma. Nontraumatic avulsion fractures in adults should be considered pathological until proven otherwise.

CLINICAL FEATURES

Obtaining the patient's history is limited due to high energy trauma. In addition to obtaining standard trauma history (AMPLE: allergies, medications, past medical history, last eaten, events leading), the mechanism of injury, location of pain, gastrointestinal incontinence, presence of neurological deficit, bleeding status, last menstrual date should be questioned..

Physical Examination

The consciousness of the patient suffering from trauma is very useful in determining pelvic fractures. Since pelvic fracture will be the result of high energy trauma, other systems must be checked. In the anamnesis taken from the patient, the location and severity of the pain, the presence of pregnancy, the brief medical history, drug use or allergy, sensitivity in the bladder or anus, last oral intake, last urine-stool output, and neurological status should be evaluated.

When starting the examination, attention should be paid to bleeding in any area, ecchymosis, and posture of the lower extremities. Edema, hematoma, ecchymosis, crepitation, incision and shape deformities in the perineal or pelvic area are important in the examination. The palpation of the bones in the area, the presence of limitation of movement, and vascular

and nerve injuries should be checked. The most important bone signs to be considered in palpation are the iliac crests, symphysis pubis, sacrum, sacroiliac joints and femur of the major thoracentric. It is checked whether there exists hematoma (destot sign) in the inguinal ligament and scrotum. Sensitivity and movement disorders in the bilateral pelvic areas, sacrum and coccyx should be evaluated.

When pelvic fractures are reviewed in general, there are two exceptional groups, which are the elderly and athletes. Sacral fractures and isolated pelvic ramus fractures secondary to osteopenia and minor traumas can be encountered in the elderly. In athletes whose bone structures are immature, avulsion fractures may occur at the point where the muscle sticks to the bone due to the sudden and very strong contraction of the muscles.

While performing the evaluation, pressure is applied from lateral to medial and front to back on the iliac wings. Pressure is applied from front to the back in symphisis pubis. Gap in the symphysis pubis may be a sign of separation. The motive power of the hip is evaluated by compressing the greater trochanter of the femur. Physical examination is very important for pelvic fractures in conscious patients [12]. Care should be taken in terms of ecchymosis, abdominal tenderness and distension while performing abdominal examination. Movement of unstable fractures should be avoided while examining the patient. Movements that will increase bleeding and cause other fractures should not be made. If there is a fracture in the pelvis, it should be assumed that there is a retroperitoneal gynecological or urological injury until retraction is performed. The incidence of severe retroperitoneal bleeding is higher in pelvic injuries which are instable like “open book” fractures and lead to separation in the sacroiliac joints. Blood coming from the external urethral meatus in men suggests a rupture of the urethra, while blood coming from the urethra and vagina in women suggests an open pelvic fracture. Rectal and vaginal examination should be checked for wall integrity, bleeding and bone fragments in open fractures. If there is a rectal injury, it especially suggests an open pelvic fracture and sigmoidoscopy may be required [13]. If there is an open pelvis fracture and organ injury, the mortality increases to 45% [14]. If there is pelvic ring disruption, 10-15% of these cases are accompanied by the damage in the pelvic nerves. The rates of neurological injury are much higher in patients with severe sacral fractures.

FIRST MANAGEMENT

First Evaluation

In all trauma patients, stabilizing the patient in terms of vital signs such as airway, respiratory and circulation is a priority. Subsequently, in primary and secondary examinations, the patient’s history and physical examination will guide us to pelvic injuries.

DIAGNOSIS

Ultrasonography (USG)

Bedside ultrasound can be performed in patients with blunt trauma. Although FAST (Focused Assessment with Sonography for Trauma) has a limited benefit, its high specificity and ability to be made at the bedside allows its use in pelvic fractures [15].

Diagnostic peritoneal lavage (DPA)

In the case of negative FAST, it determines whether the bleeding originates from the peritoneum or retroperitoneum in hemodynamically unstable patients. The presence of more than 10 mL of blood in the lavage is considered as intraperitoneal bleeding.

Plain Radiography

İf there is no complaint in the pelvis, abdomen or back and there is no tenderness in the lower parts of these regions and Glasgow coma scale> 13 there is no need for performing routine plain radiography.

According to Advanced Trauma Life Support (ATLS), an AP pelvis radiography should be performed in trauma patients who are considered to have pelvis injury. In addition, the application recommendation for diagnosis and treatment in hemodynamically stable patients is unclear [16]. Computed tomography (CT) is the main recommendation and guiding treatment. If CT is not available, portable pelvis radiography should be performed in unstable patients. Pelvis radiography is used for severe displacement fractures, open book injuries and posterior pelvis injuries. After the patient is stabilized, other special graphs such as inlet, outlet and Judet view can be performed. In the Judet view, the patient is rotated 45 degrees to both sides. Iliac and obturator oblique images are taken. This imaging guides the orthopedist before and after the surgery.

Computed Tomography (CT)

Contrast-enhanced CT is the gold standard in diagnosis due to its high sensitivity. It can show other injuries associated with pelvic injury, bleeding zone and size [17,18]. Computed tomography evaluation should also be made in patients with hemodynamically stable pelvic fractures. If we consider it to be a acetabular injury, plain pelvis radiographs will be insufficient in these patients. Therefore, performing CT should not be hesitated.

CT imaging allows for evaluating the integrity of the pelvic ligaments and measure the pelvic displacements by defining the dimensions of the fracture in three dimensions. It is also useful for planning repairs when there are fractures.

It is not safe to transport a patient who is persistently and severely hypotensive. It may not be possible to continuously monitor and manage the patient's hemodynamics. Even in hemodynamically instable patients, if needed, CT evaluation, which is the gold standard for pelvic fractures, should be postponed.

Retrograde Cystourethrogram

If there are conditions such as blood in the urethral meatus, gross hematuria in the physical examination, it is recommended to first perform a retrograde urethrogram and then a foley catheter according to ATLS.

MANAGEMENT

First Stabilization and Approach

Pelvic fractures are associated with high rates of internal injuries. Simple or serious bleeding may accompany any fracture. In the presence of a stable fracture, there is no need for an operation in general, and massive bleeding is rarely observed. Venous bleeding is more common in pelvic fractures. Arterial bleeding occurs at a rate of 10-15%, and these bleeding can cause shock or death [19]. Pelvic venous plexus bleeding constitutes 80-90% of the cases. If there is internal bleeding, massive transfusion with crystalloid fluid / blood / blood products should be started. Once stabilized, the patient should be transferred to a full-fledged hospital.

Pelvis Injury

Treatment is applied considering the type and severity of the pelvic fracture. In mild fractures, rest can be taken, ice compression can be preferred, and tools such as crutches, which assist walking, can be used if there is a need for mobilization. In case of a serious pelvic injury, the pelvis should be bandaged and fixed and the pelvic volume should be reduced. In case of fracture, pelvic packing stabilizes the fracture fragments and reduces bleeding in the area. The health personnel who will do the pelvic packing should do the pelvic ligation in the right place. It should also be avoided to bandage the pelvis too tightly. Damage by the fracture can be exacerbated with excessive reduction in pelvic ligation.

Internal rotation and taping of the legs reduces pelvic volume [10]. Linen or commercial packaging tools bandaged in a way that passes through the femur greater trochanters are also an alternative method for pelvic volume reduction [20]. Apart from linen and commercial pelvic binders, external fixators can be applied in the emergency service by experienced orthopedists or trauma surgeons. Treatment with angiographic embolization is often required in cases of degeneration in the sacroiliac joint, hypotension and women. In unstable patients with open pelvic fractures, aggressive resuscitation, tetanus prophylaxis and

broad-spectrum antibiotics are required. In order to treat the pain in pelvic fracture, pain killers from various categories can be taken. Prophylactic treatment should be started in the first 6 hours and continued for 72 hours. His/her treatment requires extensive debridement in the operating room with a multidisciplinary approach.

Emergency laparotomy and pelvic stabilization are performed for positive FAST and unstable patients. Negative FAST and unstable patients are evaluated with DPA. If DPA is positive, an emergency laparotomy is performed. In the case of negative DPA, pelvic stabilization or resuscitative endovascular balloon occlusion (REBOA) of the aorta is considered. Many unstable patients undergo pelvic angiography. However, REBOA and preperitoneal packing are more effective in bleeding control.

It will take time to move normally after surgical operations. The recovery period is prolonged depending on the general health condition of the person. Patients can obtain support from physical therapists in order to shorten this period without deformity. Various exercises can be recommended to strengthen the muscles and ligaments in the pelvic area. Nutrition and smoking are also significant factors affecting the recovery period.

The elderly are at serious risk for hidden fractures such as pubic arm fractures, and especially sacral fractures. Even if their plain radiographs are normal, but there is a suspicion of fracture, computed tomography (CT) should be performed for diagnostic imaging.

Acetabular injury

Since acetabular injuries are often accompanied by other injuries, a detailed and multi-system trauma evaluation should be made. The fracture should be treated. If there is hip dislocation, it should be placed back, and if needed, a traction pin should be placed by the orthopedist.

Avulsion Injury

It is followed and treated with rest, cold applications and analgesics. If the bone fragments are displaced more than 2 cm, surgical repair is performed [21].

Pediatric Considerations

Pelvic fractures are less common in children since their bones are more flexible. Pelvic ring fractures and avulsion fractures frequently occur. Accompanying head injuries, abdominal injuries, chest injuries, bleeding, genitourinary and neurological injuries may also be observed.

RESULTS

Pelvic traumas are generally caused by high-energy trauma and their mortality increases due to accompanying injuries. Patients with pelvic fractures should be approached as trauma patients as significant bleeding

can cause internal organ injuries. Elderly patients may have severe bleeding due to pelvic fractures occurring without any major trauma. Computed tomography (CT) is required in many injuries, since plain radiographs will not show the state of the posterior ligaments. Minor injuries such as avulsion fractures can be followed up, on condition of mobilization at home when suitable conditions are provided.

In pelvic fractures, attention should be paid to hypovolemic shock due to bleeding, and resuscitative care should be exercised starting from the first visit of the patients. Pelvic immobilization should be provided to the patients and they should be transferred to the nearest trauma center where follow-up and treatment will be done with a multidisciplinary approach. Because the situation in pelvic injuries will be more complicated than expected, early support should be received from the relevant specialist. Emergency physicians should start resuscitative procedures early and initiate appropriate consultations. In major injuries, the hospital where the patient will be transported should have a trauma surgeon, an orthopedist and an interventional radiologist.

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Chapter 28

COVID-19 TRIAGE IN THE EMERGENCY DEPARTMENTS

Asst Prof Eyup Sabri SEYHANLI[1]

1 University of Health Sciences, Mehmet Akif Inan Training & Research Hospital, Department of Emergency Medicine, Sanliurfa, Turkey
e-mail: eyyup-1976@windowslive.com

Introduction

COVID-19 disaster has become a "juggernaut" over the last year, leaving lots of people alone with lost loved ones, and continues its destruction worldwide. Nowadays, new vaccines are about to be introduced in many countries. However, unfortunately the disease progresses more rapidly than the development of vaccination. Especially lockdown, countries are taking precautions as much as their economy permits to stop this rapid spread. All these developments and measures can not reduce workload on the emergency departments. As in all other disasters, emergency departments are at the frontline of the fight against COVID-19 pandemic worldwide. However, each emergency department has its own capacity in terms of human resources, physical facilities, availability of imaging, testing, respiration equipment, intensive care etc. and when this capacity is exceeded by the demand brom both patients with suspected or confirmed COVID-19 and non-COVID patients, processing of the service begins to deteriorate. This has heavily impacted many emergency departments all over the world as well as healthcare personnel, patients, and the society from the view of the big picture, indicating necessity and critical importance of an effective triage planning in the emergency departments during COVID-19 pandemic.

COVID-19 in The Emergency Departments

The continuous spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease, namely COVID-19, which still progresses with high number of new cases and deaths, has prompted health system to prepare and arrange emergency response plans and procedures to meet surge of patients with suspected COVID-19 disease in the emergency departments worldwide. For updating, there have been 72.851.747 confirmed COVID-19 cases and 1.643.339 deaths, reported to the World Health Organization (WHO), as of 18 December 2020 (WHO 1). The COVID-19, which has been named a 'perfect storm' by some authors (Lippi), has brought an unexpected and unpredicted burden on the health system with the emergency departments being at the frontline of hospital and population based healthcare. The emergency departments along with entire hospitals and health systems are overwhelmed and their organization is highly disrupted with the devastating outbreak (Cohen). This is a challenging situation for the emergency departments that are already overcrowded under non-pandemic conditions. The emergency departments have to detect and manage patients with suspected COVID-19 on one hand, and continue to deliver emergency healthcare service to the other patients who presented with emergencies other than COVID-19 as in non-pandemic periods on the other hand.

COVID-19 outbreak has also disrupted healthcare service delivery both for patients that were infected and those who were not treated due

to the pandemic (Propper). In many countries, it has been necessary to reorganize healthcare services delivery by hospitals, and especially the emergency departments to meet patients' needs (Comelli). Unlike events that require short-term response such as weather emergencies, pandemics including COVID-19 outbreak warrant a long-term and sustained response. In order to provide a safe and effective emergency response to pandemics, the World Health Organization (WHO) published a hospital emergency response checklist in 2011. According to this checklist, an adaptation should be provided to the changed conditions of hospital emergency service, limited resources should be used efficiently and a safe environment should be maintained for emergency healthcare workers (WHO 2). The key components of WHO emergency response checklist are as follows:

1. Command and control: A well-organized command and control system is a major component of an effective hospital emergency management.

2. Communication: Clear and timely communication is necessary for informed decision making, collaboration and for raising public awareness.

3. Safety and security: Well-established safety and security plans and procedures provide maintaining hospital emergency function and efficient response operations.

4. Triage: Maintenance of patient triage operation during a disaster is essential for organization of patient care to facilitate efficient patient processing.

5. Surge capacity: Surge capacity is defined as the ability of an emergency service to deliver healthcare beyond its capacity to respond to the increased demand during a disaster. This should be addressed early enough in the planning process.

6. Continuity of essential services: Essential services such as surgery, emergency care, maternal and child care should not be interrupted due to a disaster. Essential services should continue in parallel with hospital emergency response.

7. Human resources: An effective human resources management is necessary to adequately respond to a disaster with sufficient staff capacity. In addition, healthcare staff should be psychologically supported during intense working due to an emergency. Healthcare staff should be adequately trained about the changing processing and hospital strategies during emergency situations.

8. Logistics and supply management: Hospital supply and delivery chain should be well-planned to meet increased demand in times of shortage.

9. Post-disaster recovery: Post-disaster recovery should be timely planned in order to minimize long-term impact on the hospital normal processing.

Similar disaster response plans can be developed by the emergency departments according to their capacity, intensity, physical facilities etc. Most emergency departments have been remodelled to accommodate new patient traffic due to COVID-19 pandemic. The new adjustments have affected many aspects of the emergency departments including structural reorganization and assignment of new roles to the staff. In the COVID-19 era, patients presenting to the emergency department with suspected coronavirus disease are triaged to the pandemic service, those with mild-to-severe symptoms suggesting COVID-19 are treated and managed, and care of patents with emergencies other than COVID-19 such as trauma and acute toxication is provided by the emergency department. Especially the emergency departments in low and middle-income countries have been impacted more significantly (Remuzzi) by this devastating disaster.

The COVID-19 can progress rapidly and require intensive care for patients with severe manifestations such as acute respiratory distress, hypoxia, renal failure and also vital values can deteriorate rapidly, resulting in challenges for the emergency departments (Bhatraju, Gagliano, Paganini). Because patients with suspected COVID-19 should be physically separated from other patients and transferred to special rooms and necessity of donning and doffing personal protective equipment continuously limits productivity of the emergency department staff (Ugglas). In addition, vitals of these patients should be measured and evaluated more frequently. Increased patient traffic in the emergency departments brings together the risk of negative impact on patient outcomes. Crowding due to COVID-19 pandemic has caused demand to exceed the capacity in many emergency departments, leading to an extended average waiting time (Asplin, Hoot, Hwang).

Significant risk of burnout and moral deterioration among the emergency physicians is another problem. Emergency department personnel working at the frontline are at a high risk of transmission. According to the COVID-19 pandemic data reported from Italy, the rate of infection is 10% among the emergency department workers (Liang). Working manner of the emergency service personnel also has significantly changed during the pandemic. Working hours and shifting organization has been revised to adapt the new situation. In addition, healthcare workers don and doff personal protective equipment more frequently, limiting their ability to work efficiently. On the other hand, being in an emergency department with suspected COVID-19 significantly affects patients. As is normal times, during the pandemic the emergency departments are crowded with low, moderate and high-risk patients. In order to deliver the correct healthcare

to the correct person, patients presenting to the emergency service should be classified and categorized according to the severity of their clinical picture. This is even more critical during the pandemic period, because there is a risk for non-COVID patients to be infected through the suspected patients, while patients in the emergency department have a common fear of transmission. Thus, the management of all these complex situations is the responsibility of the emergency department. Therefore, organization of emergency service processing is of paramount importance to distinguish patients according to their risks and to triage, manage and treat them.

What is triage ?

The main factor that distinguishes mass disasters such as COVID-19 pandemic from the routine management of patients presenting to the emergency department is the large number of patients that present almost simultaneously, which outsrtipt the available resources reserved for their care. However, the large numbers of patients with suspected or confirmed COVID-19 significantly impede the ability of evaluation and treatment to be delivered. Whereas, emergency services should act rapidly, allowing for a continuing influx and using the capacity efficiently.

Prioritization of emergency medical care is carried out by a process named triage, which has been derived from the French word "*triagere*", meaning "to sort". This concept was described for the first time by Baron Jean Dominique Larrey, a surgeon of Napoleon's battlefield and has become a cornerstone of medical healthcare delivery since that time (Burris, Llewellyn). Figure 1 by Louis-François Lejeune represents Baron Jean Dominique Larrey triaging the injured soldiers in the battlefield. Triage involves to match the limited resources with needs of the patients and accordingly categorize the patients to receive care based on the prioritization. The greater disaster the more challenging triage becomes, requiring more expertise and training skills (Frykberg).

Today, most emergency departments adopt a triage system to prioritize patients who are in need for urgent healthcare. As a medical term, triage is defined as "sorting of patients by giving them prioritization for treatment and transportation to other services in order to maximize the number of survivors" (Merriam). According to the Wikipedia, triage is the process of determining the priority of patients' treatments according to the severity of their condition or likely of recovery (Wikipedia).

Figure 1. *Louis-François Lejeune, Baron Jean Dominique Larrey (1766-1843)* Tending the Wounded at the Battle of Moscow, 7th September 1812.

In general, establishment of a triage system requires four conditions to be fulfilled:

A. In comparison to the need, there should be a shortage of resources to establish a reasonable triage system.

B. A system should be provided by health authorities in order to use during emergency conditions such as war, earthquake, flood and pandemic.

C. There should be trained personnel to implement a triage system.

D. Personnel should be trained on justice and prevention of personal preference in order to avoid wrong decisions when triaging the persons presenting to the emergency room.

Wrong triage

There may be mistakes in triage of the patients especially during a disaster or pandemic where the emergency department is overwhelmed by excessive burden of the patients. These circumstances almost always cause a rush and chaos that can make triage personnel prone to make wrong decisions. Wrong triage decisions can pose problems in allocation of the limited resources to wrong persons instead of those with an urgent need for medical aid. Wrong triage can be divided into two parts as ‘under-triage’ and ‘over triage’.

Under-triage is defined as “underestimating the urgency of the condition of a person presenting to the emergency department and not prioritizing the management of this person over that of another person with

less urgent needs" (Medical Dictionary 1). This is a serious condition that can cause problems in using the limited resources for a person in a really urgent condition. It was found in a study that the mortality rate was lower among the patients who were under-triaged, because blood pressure, GCS score and base deficit were better in these patients (Davis).

Over triage is defined as "overestimating the urgency of the condition of a person presenting to the emergency department and prioritizing that person over another person with more urgent needs" (Medical Dictionary 2). The risk to patients is lower with this mistake. Its effects are rather on the use of limited resources, staff, facilities etc.

COVID-19 Triage

Quick spread of SARS-CoV-2 disease, make the control of waiting areas and isolation of the rooms of patients with suspected COVID-19 from the rooms of other patients necessary to minimize the risk of spread of the virus as far as possible (Ong). Rooms of the patients with suspected COVID-19 should be separated from the other rooms and isolated according to the risk levels of the rooms. An example for the classification of risk levels in an emergency department including COVID-19 patients is given in Table 1.

Table 1. *Risk levels in an emergency department with COVID-19 patients.*

Risk Level	Classification	Examples
1. High-risk area	Dirty	Isolation rooms Examination rooms Blood collection rooms Laboratory Consulting area
2. Medium-risk area	Semi-dirty	Triage units
3. Low-risk area	Clean	Working room

The triage criteria have been dramatically changed to meet increased demand of patients seeking emergency medical aid due to the COVID-19. In a typical emergency department; entrance of the patients with respiratory problems should be separated (Huang). Contact of the patients with healthcare staff should be minimized and a social distance of 1-2 meters should be maintained. Patients at risk of COVID-19 should be detected immediately at the entrance to the emergency department and these patients should be guided to a special area (CDC1). A disinfectant and face masks should be available at the entrance and fever of all presenting persons should be measured.

When patients arrive at the hospital before admission to the triage unit, they should be questioned about the reason for attending hospital (fever, sore throat, dry cough, dyspnea etc.). At the emergency department, there should be a specific process to separate patients with suspected COVID-19 from the other patients such as waiting in different rooms, using different toilet units etc (Huang). Visual warning posters should be installed at different points of the emergency departments. These visual materials should contain the three rule for fighting against the virus, namely face mask, social distancing and hand hygiene. Patients should be provided to wait in their car instead of waiting room as much as possible in order to minimize unnecessary contact with emergency medical staff. In addition, unnecessary personnel crossing to the ED and triage unit should be restricted (CDC 2). Maximum one personnel should accompany a patient in need, if required and provided to don personal protective equipment as specified in COVID-19 instructions. Contaminated areas should be cleaned using separate cleansing tools and agents from those used to clean normal areas. Social distancing rule of about 2 meters should be applied to the patients in the waiting room. Visitors should not enter room of a patient with suspected or confirmed COVID-19 (Cao). In addition to these general rules and implementations, triage processes should be transparent and shared publicly as much as possible, because the process of triage is the responsibility of society as a whole (Herreros). The Centers for Disease Control and Prevention published a guidelines including recommendations for some common points to be considered in the planning and organization of a triage unit (CDC1, CDC2). Accordingly:

- The triage unit should be planned so that to prevent the crowd, so as the patients can enter from one side and exit from the other.
- The waiting room should be well-organized to prevent crowds from congesting the triage unit.
- Personnel working in the triage unit should be well-educated and have adequate skills to communicate with patients in different psychological conditions such as stress and anxiety about their illness.
- Protective materials such as face masks should be provided for attendants of the triage unit and a disinfectant should be available.
- Patients should follow the rule of social distancing in the case of a queue in front of the triage desk.
- Facilities at the triage unit for transfers such as stretchers and wheelchairs should be covered with disposable items.
- All surfaces at the triage unit should be disinfected at least three times a day.

On the other hand, it should be noted that the processing of a triage unit differs among the emergency departments in different countries, even in different centers in the same country based on many factors such as capacity, physical size and facilities of the center, local procedure and protocols of the hospital and/or emergency department, availability of resources including medical materials, medications, staff, monitoring and imaging devices, intensity of the infected patients, rate of new cases, referred and discharged patients.

In a triage unit, there may be healthcare workers that perform preliminary screening of the patients and do not deliver care to them. In addition, some staff in the triage unit are responsible for caring patients with suspected or confirmed COVID-19. Furthermore, patients both with and without respiratory symptoms may present to the emergency department. First of all, social distancing and donning personal protective equipment should be provided in a triage unit as shown in Figure 2.

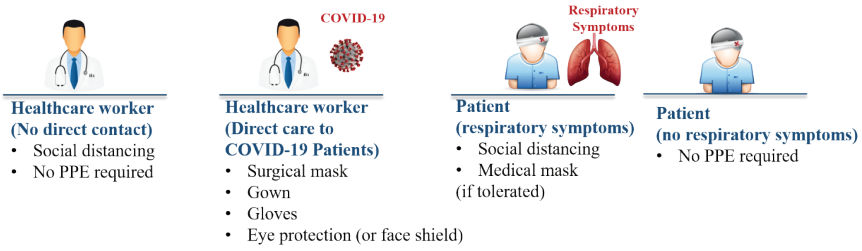

Figure 2. *Following social distancing rules (about 2 meters) and donning personal protective equipment (PPE) according to the condition of the healthcare workers and patients at the trial unit.*

When triaging patients in the emergency department, those with clinical signs and symptoms of COVID-19 and high-risk people in terms of the disease should be identified. Clinical signs and symptoms of COVID-19 include direct contact with a confirmed COVID-19 patient, travel to abroad within the past 14 days, fever ($\geq 37.3^{o}C$), dry cough, sore throat, shortness of breath, headache and gastrointestinal complaints such as nausea and diarrhea. Whereas, high-risk persons include those aged over 60 years, patients with hypertension, diabetes mellitus, chronic liver disease, chronic renal disease, cardiovascular disease, immunodeficiency, those receiving immunosuppressant drugs and persons with a body mass index (BMI) > 40 Kg/m^2 (WHO 3).

What to observe in an efficient triage process

As above mentioned, the triage process differs among emergency departments, although there are some common point to be addressed for a rapid, safe and efficient triage:

1. First of all, take standard measures including hygiene, safe waste management and using personal protective equipment.

2. Perform risk assessment of the patient (airway and circulation).

3. Receive a history of COVID-19 symptoms such as dry cough, fever and dyspnea from the patient.

Primary goal of the initial assessment is to quickly obtain information (including subjective data). Then the triage personnel should refer the patients to the waiting, examination or isolation room based on the initial assessment (Schwartz). Emergency staff involved in the transfer of the patient should be educated on how to use personal protective equipment during the referral. In order to stop further spreading of the disease in the emergency room setting, top priority patients should be sent to isolated areas. There should be a protocol between the emergency department and emergency medical service (EMC) to be implemented in case of the transfer of an infected patient to the hospital with an ambulance. The personnel who care for patients with suspected COVID-19 patients should not deliver care to the other patients to prevent transmission. The triage unit should be supported by other healthcare workers at the times of congestion.

Conclusion

The triage processing in the emergency department is of critical importance because of the overcrowd setting due to patients presenting with the suspicion of COVID-19. The emergency departments are at the frontline of the fight against the virus. In order to prevent delays in guiding patients to other services or intensive care, if necessary, to provide rational and efficient use of the limited resources, and to protect both medical staff and patients from transmission, triage process should be performed rapidly and safely. Healthcare staff working in triage units should be adequately educated about the process including effective communication with patients that are in a stressful and anxious state due to their conditions and fear of their symptoms. When a triage procedure is implemented properly and effectively, this will reflect on organization and processing of the entire emergency service, providing significant contribution to struggle with this devastating disease.

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Chapter 29

BIOSIMILARS: PRODUCTION, MANUFACTURING AND MARKETING ASPECTS

Semih Latif İPEK[1],
Dilek GÖKTÜRK[2]

1 Adana Alparslan Türkeş Science and Technology University, Engineering Faculty, Food Engineering Department

2 Adana Alparslan Türkeş Science and Technology University, Engineering Faculty, Bioengineering Department

Health is a typical area where market competition economic theory does not benefit. To give a typical example, the pharmaceutical market is one of the most important areas facing failure due to the lack of price competition. Various solutions have been developed to overcome this problem, such as reimbursement or government intervention, which are more intense than other products in comparison. Research and Development (R&D) activity shapes the pharmaceutical market in terms of pricing, and upcoming drugs are protected by patents to reward investments. When the patent expires, the original drug can be copied by other companies. This situation strengthens the establishment of biosimilar drugs in the pharmaceutical market (Garattini, Curto, & Vooren, 2015). It should be emphasized that biosimilars are not biogeneric, but a form of replicated medicinal drug or protein drug. The difference is due to the manufacturing process, method or cell line produced by the drug (Nowicki, 2007). The aim of this article is to show the opportunities of biosimilar drugs that can provide more affordable and useful pharmaceutical products for all walks of life.

Biosimilars, also known as biopharmaceuticals, are drugs derived from yeast, bacteria, cells or other biological products to use as efficiently and safely as original drugs. The popularity of these drugs has increased in recent years due to their low cost. On the other hand, biosimilar production is based on a complex process and is difficult to reproduce. This point raises a question about regulatory issues. For example, a small change in process can cause a dangerous change in biosimilar drug quality and safety (Steinberg et al., 2019).

Considering the immunogenicity and complexity of biosimilars during the manufacturing process, a number of regulatory approval procedures must be followed. Biosimilars are more vulnerable to acute and chronic immune reactions due to their protein content. Biosimilars must be designed to have equal protection and efficacy with respect to biological materials of the reference mark, but are not standardized equivalents of the original compounds and are therefore not interchangeable. Biosimilars, as a result of these distinctions, require class-specific regulatory approval pathways that require the availability of clinical trial results demonstrating appropriate behavior and protection (Dranitsaris, Dorward, Hatzimichael, & Amir, 2013).

In the biosimilar field, there are a number of important problems, including (i) assurance of similarity, (ii) interchangeability between biosimilars and new drugs, (iii) the potential need for private labeling to distinguish between various biopharmaceutical products (iv) regulatory structure, (v) commercial opportunities and guidance to assist manufacturers in product growth (Sekhon & Saluja, 2011).

A specific business policy should be designed for pharmaceutical companies that plan to produce a biosimilar product before the production

process. The strategy should include both the targeted consumer segment and the value proposition provided by the biosimilar commodity. It will take a long time to improve biological facilities, produce and market drugs, and this may delay the production and introduction of biosimilar products. (Dewi, 2018).

The purpose of this review is to help patients and healthcare teams make well-informed choices in health care strategies regarding the use of biosimilars. As the biosimilar market matures, more studies will be required.

Production of Biosimilars

Biosimilars go through a manufacturing process that requires high technological methods and scale-up production styles. Since the biosimilar must have similar characteristics with the generic product, a separate gene related to the product is isolated at the first stage in the production process. The isolated gene is then inserted into a vector. The most preferred method is cloning into circular DNA vectors. After this step, a suitable host cell is used for cell expression. Yeasts and E. Coli are some of the most used host cell varieties in production of biosimilars. Cell culture procedures are applied to propagate host cells. After cell culture characterization, a rigorous work is done for a protein purification step followed by a protein production step using chromatography methods. Necessary analyzes and formulas are made for commercial use, and biosimilar drugs are best stored and used until use (Dranitsaris et al., 2013). The flow chart of production of biosimilars is shown in Figure 1.

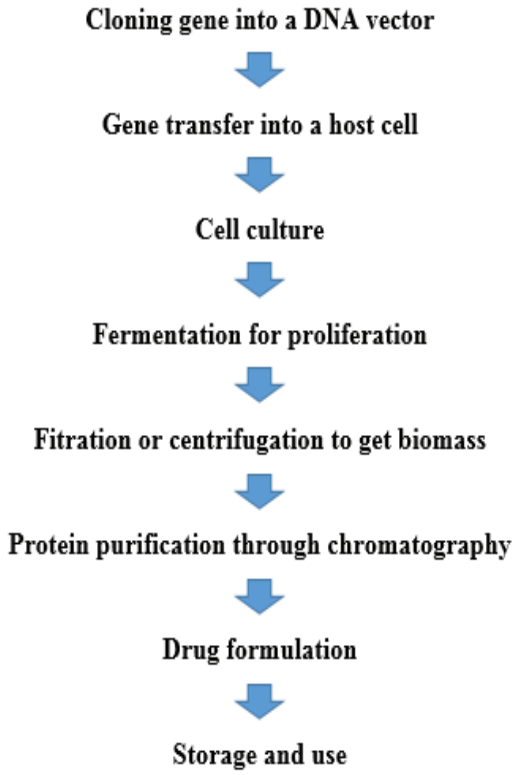

Figure 1. Flow chart of production steps of biosimilars (Dranitsaris et al., 2013).

Manufacturing and Marketing Aspects for Biosimilars

Biosimilar fabrication is a landmine with legal, manufacturing and marketing challenges, making it one of the most costly development ideas in the pharmaceutical industry. Price reductions are the main reason for using biosimilar products rather than the first product. Biosimilars offer patients access to more cost-effective options and will promote a favorable climate for the future production and commercialization of biological drugs. Promoting the production of biosimilars appears to be an important opportunity. But understanding the driving forces of biosimilars is a major challenge at this stage. Biosimilars are not replicas of the reference product, therefore pre-clinical and clinical studies of biosimilar products should be performed using an approved reference product as a control. On the other hand, biotechnological drugs will become an important part of the health sector and that the increase in the number of biological products and biosimilar drugs will provide alternative therapies and increase the access opportunities of patients by reducing treatment costs (Nacak, Sezer, & Erenmemişoğlu, 2012).

In 2005, a year before the first biosimilars were authorized, the European Medicines Agency was the first regulatory body to set standards for biosimilars. The Member States of the European Union have the authority to enforce all kinds of laws on the processing, growth and authorization of biosimilar products. This structure was previously adopted by the World Health Organization (WHO) in 2009. The WHO Biosimilar Regulatory System has approved internationally accepted requirements for the market introduction of safe, reliable and comparable quality biotherapeutic products. The main purpose of the WHO regulatory system is to support and ensure that local regulatory authorities meet international biotherapeutic development requirements. These guidelines were later adopted by other countries on their own, but few allowed their own guidelines based on existing models (Kabir, Moreino, & Siam, 2019). While biosimilars will potentially reduce the costs of modern treatments, there are issues that need to be addressed by physicians especially with regard to the differences between biosimilars and classical chemical drug generics, the need for adequate regulations and the identification of possible problems with biosimilars. From the point of naming problem, The International Nonproprietary Name (INN) system was introduced by WHO in an aim to name active substances via guidelines for international naming to provide safe prescription medicines (Declerck, 2007). An example list of some approved biosimilars and their INN equivalents are given in Table 1 (Bressler & Dingermann, 2015).

Table 1. *An example list of some approved biosimilars and their INN equivalents (Bressler & Dingermann, 2015).*

Biosimilar	INN	Reference Product
Abasria®/Lilly/Boehringer Ingelheim	Insulin glargin	Lantus®
Benifaio®/Finox	Folitropin	Gonal-f
Inflectra™/Hospira Remsima®/Celltrion	Infliximab	Remicade ®
Nivestim™/Hospira	Filgrastim	Neupogen®
Retacrit™/Hospira Silapo®/Stada	Epoetin	Eprex®
Omnitropin®/Sandoz	Somatropin	Genotropin®

Thanks to this name system, the same chemical formula produced from different sources or procedures was given to the same but not internationally registered drug. It was also stated that biosimilar compounds have different origins and should have the same effect on patients. The limited clinical familiarity of biosimilars and comparability activities to date require the inclusion of adequate measures to ensure patient safety in their use (Declerck, 2007). Three key things should also be considered, including substitution, pharmacovigilance and traceability issues. It should be highlighted that generic drugs are never the same as biosimilar drugs due

to their nature and production methods, and biosimilar drugs are produced from different biotechnological production systems from prokaryotic and eukaryotic cells. In addition, biosimilars may have greater molecular weight than generic drugs, differ in many aspects such as the degree of glycosylation, post-translational changes, missing protein ratio and yield. Apart from these distinct properties, it is critical to implement a guidance governing the promotion and management of biosimilars. This will dispel unfounded doubts and make it easier to better exploit the therapeutic and economic opportunities provided by biosimilars. However, the need for these recommendations does not distract attention from the great opportunities offered by the launch of biosimilars (Genazzani et al., 2007).

Europe and the USA are also reviewing clinical trial criteria for acceptance of biosimilar products. Various design types for clinical research that will be important in the production of biosimilars. A number of trials have been conducted on two recently announced and marketed biosimilars, biosimilar CT-P13 (Remsima) to infliximab for rheumatoid arthritis patients, and CG-10639 to pegfilgratstim, an albumin-dependent colony stimulating factor for produced treatment for neutropenia. With the interpretation of the results of randomized studies against these biological substances, these two biosimilars have been shown to have comparable safety and efficacy in the treatment of diseases (Dranitsaris et al., 2013).

Biosimilars are drawing an economic attention, taking into account prices, generics and protection properties. The researchers concluded that biosimilars may lower prices compared to original drugs, but their benefits may not be as high as seen for traditional generics (Roger & Goldsmith, 2008). There are critical concerns considering current state of regulatory approval processes and potential opportunities for specific medicinal product formats which needs to be addressed. On the other side biosimilar research will pave tha way for novel biopharmacutical products such as anticipated humanization of yeast N-glycosylation pathways. This will enable to produce precisely glycosylated bioactive proteins for therapeutic aims without using mammalian cell cultures (Roger, 2010). As the cancer figures substantially increase over the world, oncological drug cost rises as well. This might cause a dangerous situation that to become cancer drugs unaffordable. Biosimilars are seen as cost saver as a measure against high prices in drugs in this respect. Many developed countries are running special programs to enter biosimilar drug into healthcare systems to alleviate price pressure on drugs. Delaying the use of biosimilars in the healthcare system may lead to the risk that prescription drugs may not be covered by the health system in the near future (Cornes, 2012). Up to date U.S. Food and Drug Administration (FDA) approved biosimlars list is given in Table 2 (Biosimilar Product Information, Accessed in 20.12.2020 (https://www.fda.gov/drugs/biosimilars/biosimilar-product-information)).

Table 2: Up to date FDA approved biosimlars list. (Biosimilar Product Information, Accessed in 20.12.2020 (https://www.fda.gov/drugs/biosimilars/biosimilar-product-information)

Biosimilar	Approval Date	Reference Drug
Riabni (Rituximab-arrx)	December 2020	Rituxan (rituximab)
Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)
Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)
Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)
Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)
Ziextenzo (pegfilgrastim-bmez)	November 2019	Neluasta (pegfilgrastim)
Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)
Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)
Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)
Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)
Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)
Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)
Ontruzant (trastuzumab-dttb)	January 2019	Herceptin (trastuzumab)
Herzuma (trastuzumab-pkrb)	December 2018	Herceptin (trastuzumab)
Truxima (rituximab-abbs)	November 2018	Rituxan (rituximab)
Udenyca (pegfilgrastim-cbqv)	November 2018	Neulasta (pegfilgrastim)
Hyrimoz (adalimumab-adaz)	October 2018	Humira (adalimumab)
Nivestym (filgrastim-aafi)	July 2018	Neupogen (filgrastim)
Fulphila (pegfilgrastim-jmdb)	June 2018	Neluasta (pegfilgrastim)
Retacrit (epoetin alfa-epbx)	May 2018	Epogen (epoetin-alfa)
Ixifi (infliximab-qbtx)	December 2017	Remicade (infliximab)
Ogivri (trastuzumab-dkst)	December 2017	Herceptin (trastuzumab)
Mvasi (Bevacizumab-awwb)	September 2017	Avastin (bevacizumab)
Cyltezo (Adalimumab-adbm)	August 2017	Humira (adalimumab)
Renflexis (Infliximab-abda)	May 2017	Remicade (infliximab)
Amjevita (Adalimumab -atto)	September 2016	Humira (adalimumab)
Erelzi (Etanercept-szzs)	August 2016	Enbrel (etanercept)
Inflectra (Infliximab-dyyb)	April 2016	Remicade (infliximab)
Zarxio (Filgrastim-sndz)	March 2015	Neupogen (filgrastim)

European interactions with Erythropoiesis-Stimulating Agent (ESA) Eprex (Epoetin Alfa) and Granulocyte colony stimulating factor (G-CSF) Neupogen (filgrastim) biosimilar drugs in five countries, including Germany, the United Kingdom, Sweden, France and Italy were investigated for the possible potential applications of biosimilars in Europe and the United States. A notable result is that the comparative output of biosimilars evaluated in Europe is mixed across countries and goods. While a shared regulatory framework for the approval of biosimilars is in place in the European Union, differences in payment practices and benefits, and differences in medical practices have contributed to varying results between countries. It is impossible to generalize the various healthcare programs, but the cases closest to the United States are probably provided by Germany

and Sweden. Both countries have relatively high costs for new prescription products, a tradition of generic use, and a fragmented approach to the use and payment of drugs. This suggests that after a transition phase biosimilars can gain large shares in the United States compared to reference products. The second important conclusion is that the cost savings resulting from the introduction of biosimilars in the European countries studied, competition is limited to first-generation reference products in the ESA and G-CSF categories, and longer-lasting second-generation models typically have leading shares in these categories (Grabowski, Guha, & Salgado, 2014).

The impact of cost reduction initiatives on the biosimilar drug market are a feasible and cost-saving tool for minimizing spending on health care. In Italy, due to the cost containment measures, physicians started to prescribe biosimilars more. The most prescription of biosimilar was seen in Campania region. On top of that, biosimilar prescription figures raised all over Italy. The penetration of biosimilar drugs in Italy shows that they stand as a strong alternative for affordable drug (Menditto et al., (2015) .A differentiated selection experiment of gastroenterologists was conducted to reveal clinicians' initial and biosimilar treatment preferences in ulcerative colitis. The selection task identified hypothetical situations in which certain advantages were achieved in terms of access to biological medicine using the biosimilar treatment option. It was concluded that, although most gastroenterologists have reservations about the use of biosimilars, they are likely to explore biosimilar treatment options in exchange for better access to biological therapy (Baji et al., 2016). Post marketing surveillance is an important part of pharmacovigilance that ensures safety for patients in use of biosimilars. Pharmacovigilance monitors and evaluates medications all drugs in case a measure against their change of risks or adverse effects to take necessary measures. Biosimilars are in priority list of pharmacovigilance due to their long term effects on patients are not yet known. In this respect European Union added biosimilars into 'List of Drugs Subject to Additional Monitoring' for further investigation for possible adverse ora another effects of biosimilars (Francescon, Fornasier, & Baldo, 2016). Seven European countries - Belgium, the Netherlands, Germany, Italy, France, Norway and the United Kingdom and the United States are discussing policy responses to competition between biosimilars and generics. These countries draw on findings from a range of post-market strategies and previous studies. They also address biosimilar measures in terms of interchangeability, doctor order, substitutability, distribution to pharmacists, financing for clinics, and tendering and pricing. Despite the similar policies and regulations for approval biosimilar that paves the way for removal barriers of competition in developing biosimilar drugs, differences in premarket regulations and unknown interchangeability of biosimilars cast a shadow on competition between these biosimilar drugs as their competitors, generic drugs. Governments should

give incentives and exclusiveness for interchnageability studies for biosimilar drugs (Renwick et al., 2016).

While several studies have identified possible drivers and limitations to adopt biosimilar drugs, most have evaluated the link between biosimilar market trends and the characteristics of different countries, such as drug policies and economic characteristics, using a qualitative approach. Moreover, while there are very few biosimilars on the market, these studies have been conducted generally. In one study, researchers did not attempt to classify biosimilar uptake factors in a multivariate model that combines biosource deduction and biosimilar acquisition rewards. In this sense, a comparative study was conducted on the impact of biosimilar award policies on the adoption of all applicable biosimilars in the EU, taking into account other factors, including the cost difference between biosimilar and source commodity, sales system, generic (Rémuzat et al., 2017). Rémuzat et al. (2017) developed a three-step method to identify primary factors for the uptake of biosimilars: (1) a literature review to identify incentive policies in place to increase the uptake of biosimilars in selected countries; (2) evaluation of biosimilar market trends based on database research; and (3) regression model analysis.

Biosimilars are determinants in many aspects of oncology, increasing patients' access to treatments, and contributing to the survival of health systems. The need for a complete pharmacovigilance action plan necessitated another agreement between regulatory authorities for biosimilar medicines worldwide. The primary goal of this action plan will be to evaluate the effectiveness of drug function. Studies with non-equivalent findings are important for documenting and comparing long-term side effects. The development of reliable biosimilars by all healthcare providers for oncology patients should be a major commitment (Gifoni, Fernandes, & Chammas, 2018). In some countries, pharmaceutical companies have manufactured biosimilar drugs and used them as therapy in the therapeutic setting. Since its introduction the following biosimilar issues have been discussed: safety risks, biosimilar classification, biosimilar naming scheme, reduced unit cost, price competitiveness, increased volume. In addition, there are biosimilar formulation issues (Dewi, 2018). Adalimumab, etanercept, and infliximab biosimilars are available for psoriasis patients. A discussion of dermatologists and biosimilar manufacturing and scientific concepts that treat and/or control psoriasis, and described their experience with accessible biosimilars in dermatology that will enable doctors to make better treatment decisions for psoriasis patients. Biosimilars can also provide cost savings as a lower cost alternative to source biologics that can be reinvested in the creation of new treatment alternatives for psoriasis patients (Carrascosa, Jacobs, Petersel, & Strohal, 2018)

European markets that have witnessed biosimilar drug competition since 2006. Biosimilar entry, price, and penetration are expected by

consumer characteristics and public policies, and found significant heterogeneity between nations and items have been examined. In addition, the penetration of biosimilars has also been investigated. As a proportion of total revenue, there is a clear trend for biosimilars to grow over time, with an annual increase in biosimilar penetration by about 5.5 percentage points each year. There is considerable heterogeneity in this overall increase in prevalence: the biosimilar penetration of epoetin is increasing by about 9 percentage points per year; the biosimilar penetration of filgrastim increases by about 4.1 points per year, while the biosimilar drug penetration of somatropin increases by about 2.6 points per year (Morton, Stern, & Stern, 2018). Biosimilars are expected to be cheaper than biologic drugs. However the cheapness is projected to be between 10-20% due to the process and development cost that makes companies avoiding to enter into the biosimilar sector. Additionally, the biosimilars industry still faces many challenges in terms of manufacturing, pricing and market access, immunogenicity, cost effectiveness and quality. However, the demand for biosimilars is currently one of the most profitable markets and is expected to grow rapidly over the next decade (Farhat et al., 2018).

By analyzing their structural similarities and biological functions, Gianoncelli et al. (2019) focused on pairing the creator of filgrastim with three biologics. In this study, Nivestim™, Tevagrastim®, and Zarzio® and the reference product Granulokine® were evaluated qualitatively and quantitatively using RP-HPLC-UV, MALDI-TOF/TOF-MS instruments for molecular analysis and zebrafish embryo for in vivo studies. Experiments showed that four drugs have the same amino acid sequence and same effect on zebrafish embryo. The structural similarity of biosimilar drugs and their constituents has been demonstrated by numerous studies conducted in this report. A similar biological behavior in the living creature further supported this finding. It was sought to collect and evaluate all published applicable intelligence on the health of biosimilars and market prospects. In the biosimilar development process, it is important to maintain rigorous production and quality management processes. The advent of biologics and biosimilars, together with the continued growth in healthcare expenditures, will provide a solution to improve patients' access to biotherapeutic treatment. However, healthcare providers and consumers need to be more familiar with these drugs and to achieve their fully expected effects within the healthcare system (Kabir et al., 2019). A provisional financial review of the impact of biosimilar application on corporate procurement expenditures was introduced by Mezones-Holguin et al. (2019). Financial studies reveal that the application of biosimilars saves money on academic spending transactions. Hence, based on the cost-opportunity theory, the replacement of Infliximab with its biosimilar has become a legitimate therapeutic solution in Peruvian Social Security (Mezones-Holguin et al., 2019).

Biosimilar drugs in inflammatory bowel disorders have been studied by Kaniewska et al. (2019). With comparable potency and efficacy and lower drug rates, biosimilar drugs encourage patients to gain greater access to clinical therapy. Clinical studies have shown that switching from a reference drug to a biosimilar drug will not alter the effectiveness of treatment and the likelihood of complications. However, there is no evidence as to what happens in the therapy process, whether there are frequent switches between reference and biosimilar drugs or between separate biosimilars (Kaniewska et al. 2019).

Identification of serum Infliximab and its biosimilars was compared to four immunological tests commercially available. In addition, typical immunodominant epitopes were determined by an appropriate evaluation of the recovery of reference infliximab and its biosimilars at serum concentrations of the identified infliximab antibodies. The observed deviation is clinically negligible between the first drug and biosimilars and is less than the normal methodological heterogeneity observed with these approaches. Quantification of biosimilars and Infliximab was similarly affected in sera containing antibodies to Infliximab. As a result of four different immunoessays, infliximab therapy can be adequately conducted by biosimilars (Neveu, Kunst, Prosser, and Robitaille, 2020).

Current awareness and perceptions of healthcare practitioners on biosimilar prescribing and built their questions on this is analyzed. Considering that every country has biosimilar purchasing and pricing practices, it was aimed to examine the current experience, behavior, and understanding of healthcare professionals involved in biosimilar prescribing between 2018 and 2020. In an effort to integrate regulatory, therapeutic and research elements, the proportion of Biosimilars goes further. This report shows that initiatives and incentives are needed to establish evidence-based continuing biological therapy education services. This will serve to increase understanding not only at the therapeutic level, but also at the molecular levels of biosimilars (Halimi et al., 2020).

Comparatively contemporary application of biosimilars in pharmaceutical therapy has created the need to establish step-by-step approval procedures for these agents before they can be commercialized. There is a combined priority to maintain a high degree of similarity with the creator meta. The approval process for biosimilar drugs requires rigorous comparability studies to assess their consistency, clinical benefit, pharmacological action, and protection of use. This approach affects the assessment techniques that begin with the physical, biological, and chemical properties of the substance up to the evaluation of its effectiveness in in vivo clinical and non-clinical tests. Improving access to biosimilars and ensuring their successful use in therapy requires a strong degree of cooperation between various actors playing a different role in the regulatory pathway. There is an increasing need to increase the capacity of regulatory

authorities, as they have a crucial role to ensure the commercialization of healthy, high quality and efficient biosimilars (Kabir et al., 2019).

Conclusion

The world market has opened its doors to clones of biological products after the patent term of first generation commercialized biosimilar drugs has expired. Biosimilar products aim to promote unique access to a wide variety of life-saving biological materials. However, to fulfill this commitment, it is important to increase the production of biosimilars with safe, predictable regulatory mechanisms and sustainable policies. It is important for healthcare and marketing practitioners to know the basic complexities of biosimilar use and to apply appropriate therapeutic and commercial choices. There are active discussions around the world about problems with biosimilars. A critical assessment is required for more reliable, cost-effective and widespread availability of biosimilars.

It is anticipated that the introduction of biosimilar products that have been manufactured using carefully controlled methods, have been extensively evaluated in extensive clinical trials, and have significant post-marketing safety evidence, can lead to their adoption. In this context, proper reporting by healthcare practitioners and fair and impartial sharing of evidence will be necessary to make appropriate prescribing decisions. It should be noted that the failure of biosimilar medicines can entail a huge expense for the companies and health systems that produce them, as decreasing of drug prices depend on patent expiry and the existence of competition

As more biologic products are out of patent, more biosimilar will be available on the market and the market will gain interest. Therefore, more research is needed. This is a very competitive business environment and therefore policy makers must closely monitor the market to keep up with changes in the drivers of biosimilar demand. The path of the biosimilar industry should be to improve and adjust the regulatory mechanisms that decide their position in the healthcare field.

Within the scope of investment in research and development activities, the question of sustainable use of biosimilars can be elucidated by more precise process development. Accordingly, universities, private companies and public health institutions should cooperate in this perspective to accelerate the work, and politicians should prioritize biosimilar drug funds because of the strategic future that can save lives with less cost. In addition to its health and scientific benefits, biosimilar drug production should be supported as it is mostly needed by foreign countries in the pharmaceutical market. In addition, research and development studies should take into account production costs, which increase the overall cost of manufacturing biosimilars and prevent them from being a good competitor to other drugs.

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Chapter 30

COMPARISON OF INSTALLED LIDOCAINE IMPACTS ON PAIN MANAGEMENT IN DOGS UNDERGOING ABDOMINAL SURGERY

Murat KİBAR[1]

1 Artvin University, Artvin Vocational School, Department of Forestry, Hunting and Wild Life Programme, Artvin 08100, Turkey.

Corresponding author: muratkibartr@yahoo.com

Introduction

Ovariohysterectomy (OVH) is one of the most commonly performed surgeries in general practice and is considered to be a moderately painful procedure.[1,2] Anesthetic techniques for sterilization range from local anesthesia to neuraxial or general anesthesia.[3]

Lidocaine is a mild local anesthetic and antiarrhythmic agent that has been used for years in canine clinical practice to provide loco-regional analgesia and to treat ventricular dysrhythmias. Lidocaine inhibits the neurons responsible for visceral pain transmission.[4]

Although previously investigated for intraoperative pain relief,[4,5] use of local anesthetics have not been compared for postoperative pain relief in animals undergoing elective OVH. Animals requiring OVH procedure constitute the most common type of clinical case referred to veterinary clinics. Because it is so common, the present study includes this type of procedure so that the result may be useful for small animal practitioners. The objective of the research was to investigate and checked the analgesic level of installed intraperitoneal lidocaine during the perioperative and postoperative times in dogs with abdominal surgery.

Materials and methods

Eight intact female dogs (weiging between 5.5 and 18 kg, and from 7 months to 8 years in age) referred for the OVH procedure from a dog care house at regular during 2 months were included in the study. Animals judged to be healthy upon clinical examination by the lead investigator were included (American Society of Anesthesiologist's classification I, ASA). For each dog, age, body weight, ASA physical status, sexual cixlus, and duration of operation were recorded. All dogs were discharged 24 hours after the operation.

Dogs were premedicated with xylazine IM, 2 mg/kg. Anesthesia was induced 15 min after xylazine injection using ketamine IM, 10 mg/kg. Either the right or left cephalic vein was cannulated using a 20 or 22 G over-the-needle catheter (Bıçakçılar, Turkey) for the performing of the subsequent blood sampling. Electrocardiogram, non-invasive blood pressure (BP), respiratory rate (RR), heart rate (HR), pulse oximetry, and rectal temperature were monitored (Guoteng Co Ltd, China) continuously throughout the anesthesia.

All operations were made by the one ginecolog with helping from 5th class faculty of veterinary medicine students. The dogs were included with eight dogs in group. After the laparotomy the group L applied intraperironeal instillation of 3.5 mg/kg (lidocaine 0.2%). To apply the local anesthetic intraperitoneally, sterile injectors (23 G) were used. The

lidocaine was applied over the area of uterine stump, broad ligament, and ovaries. The local anesthetic was received at the same time in other ways so that it would reach the cranial, caudal, right, and left areas of the urogenital area. The control group applied 1.75 ml/kg of intraperitoneal serum physiologic in a samely method. The operative time was defined as the time elapsed between the first incision and the last suture.

During the research, pre and postoperative pain was evaluated at T0 and then at 0.5, 1, 2, 3, 8, and 24 hours in postoperative time. The same researcher, who was blinded of the dogs' group include, assigned the pain behaviors of all dogs using the short form of the Glascow Composite Measure Pain Scale (CMPS-SF).[6] A total pain score was calculated for each time point. To control the severity of postoperative pain, if a dog was evaluated CMPS-SF > 6, IV carprofen IM was planned to give as a rescue anelgesic.

Heparinized blood samples (4 ml) were provided from the indwelling catheter in the sephalic vein. Blood samples tested for plasma glucose were centrifuged at 1500 g for 10 minutes at room temperature' the plasma was removed, and the blood samples were stored at -80 °C in labled Eppendorf tubes, and then controlled for glucose level at the end of the research by a general laboratory using a BA-88A Semi-Auto Chemistry Analyzer (Mindray, China).

ANOVA and Tukey's multiple range tests were used to assess the differences between the groups. The SPSS software program (Version 12.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The study protocol was approved by the local ethics committee (approval number: 2014-12).

Results

Subjects from the two groups were similar in age (2.63 ± 0.8 years in group L, 2.38 ± 0.2 years in the control group) and body weight (group L,10.13 ± 1.12 kg, control group, 10.00 ± 0.71 kg). There were no significant differences, and it was thus obvious that the dogs had been placed in the different experiment groups by chance. The duration of surgery was 25-30 min. The stages of the sexual cycle in dogs were determined as follows:11 dogs in anoestrus, 3 dogs in prooestrus, 1 dog in dioestrus, and 1 dog in metoestrus.

There were no significant differences between the experimental groups taking intraoperative monitoring values (mean ± SE). All of these values were within the respective reference ranges for anesthetized dogs (Table 1). Mean (± SE) systolic, mean, and diastolic BP values increased 20% in the control group following the ligation procedure (Table 1, T2

time point). All of the dogs woke from the anesthesia normally and without complications. With the exception of subjects receiving trimetoprim + sulfonamide, all were received as a single dose.

There were important differences (P<0,05) in CMPS-SF among the experimental groups. In the preoperative period, all animals had a CMPS-SF point of 0. groups L had significantly lower CMPS-SF scores than the CN, at the 0.5, 1, 2, 3, 8, and 24 hour after operation (Table 2). The highest and lowest CMPS-SF values were determined at 2 h (6.00 ± 0.71) and 24 h after surgey (2.38±0.37) in group L. Likewise, the highest and lowest CMPS-SF values were determined at 0.5 h (8.88 ± 0.54) and 24 h after surgey (6.88 ± 0.48) in the control group. The CMPS-SF scores were >6 for the 8 and 3 dogs in group C and group L, respectively. Therefore rescue analgesic was used in these dogs.

Table 3 demonstrates the mean (±SE) plasma glucose levels at time points. Glucose levels piked at 3 h in group L and the control group. Glucose levels differed significantly at 3 and 8 h for group L when measured against the control group (P<0.05). Thus, the glucose concentration reduced more quickly in group L than in the control animals. Only the concentrations at the 3 and 8 h time points were important (P<0.05) higher than the T0 level in the control. After 24 h, the glucose levels were near T0 levels in the control animals, while the levels were not importantly high for group L. The concentrates for the 3, 8, and 24 h time points not imporatantly (P>0.05) differ from the T0 concentrate in group L.

Discussion

Lately there has been concern over the use of peritoneal application of local anesthetic drugs in terms of pain managament in the postoperative period in veterinary practice.[7] This prospective, randomized, double-blind, placebo-controlled study has estimated and demonsrated the potential of a lidocaine to conduce a stable and balanced plane of postoperative analgesia for up to 24 h in ASA status 1 patients. The lidocaine regimen was also shown to be tolerated well critically, even among a population of dogs classified as ASA status 1 with previously open surgery of abdomen. Different analgesic levels and effects obtained by using various lidocaine doses have not yet been determined in a clinical study.

Though lidocaine are unlikely as a first-line analgesic drug for use in animals after surgical procedures, our finding show that these drugs should be noted as reliable and well-tolerated analgesics when administered. In conclusion, installation of lidocaine obtained satisfied analgesia, and it could be used for pain management intraoperatively and after abdominal surgery procedures such as OVH in dogs.

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Table 1: *Distribution of intraoperative monitoring values in dogs (Mean±SE).*

Parameters/Groups		T1 (5 min)	T2 (10 min)	T3 (15 min)	T4 (20 min)	T5 (25 min)	T6 (30 min)
O2 SAT (%)	**Control**	90.13±1.4	91.63±1.53	87.25±1.78	88.88±1.50	90.25±1.79	89.43±2.09
	Lidocain	90.13±1.9	91.25±1.75	89.75±1.37	91.38±0.80	90.63±1.02	87.29±5.10
Respiration rate	**Control**	14.50±1.6	13.88±0.48	14.00±1.12	14.63±0.71	14.00±1.04	14.43±0.84
	Lidocain	13.13±1.2	14.75±2.83	11.50±0.53	12.13±1.48	11.63±0.46	14.14±1.40
Heart rate	**Control**	77.88±6.56	87.38±7.34	83.63±7.97	74.13±6.73	68.38±8.77	75.14±14.07
	Lidocain	67.13±10.41	60.63±13.26	69.38±9.72	64.13±8.80	62.63±7.44	78.71±13.51
Pulsation *(sistolic)*	**Control**	124.13±6.19	168.88±10.3	160.13±10.1	158.25±9.84	147.25±7.91	141.43±7.67
	Lidocain	134.13±9.09	135.8±8.35	132.50±9.86	133.13±7.51	122.13±7.69	124.43±8.97
Pulsation *(mean)*	**Control**	107.13±6.22	144.25±10.8	140.13±9.72	134.63±10.0	126.38±8.38	123.43±7.98
	Lidocain	106.50±9.00	107.63±9.06	109.13±9.57	108.50±7.53	100.50±6.72	108.71±7.17
Pulsation *(diastolic)*	**Control**	93.00±4.68	126.88±7.78	120.25±7.54	118.75±7.32	110.50±5.90	106.00±5.81
	Lidocain	94.25±9.26	96.50±9.10	92.25±8.34	96.50±5.67	96.75±6.26	98.29±7.73

Table 2: *Mean CMPS-SF scores from each groups of dogs at each time point (Mean±SE).*

Groups	Postoperative					
	30 min	**1.hr**	**2.hr**	**3.hr**	**8.hr**	**24.hr**
Control	8,.88±0.54 ^{A}	8.50±0.58 ^{A}	8.00±0.44 ^{A}	7.00±0.53 ^{A}	7.00±0.41 ^{A}	6.88±0.48^{A}
Lidocain	5.75±0.78 ^{aB}	6.00±0.33 ^{aB}	6.00±0.71 ^{aB}	4.00±0.37 ^{aB}	2.50±0.37 ^{bB}	2.38±0.37^{bB}

^{abc} means with different superscripts within one row differ significantly ($p < 0.05$)

^{ABC} Different letters in the column indicate the significant differences ($P < 0.05$)

Table 3: *Plasma glucose levels (means±SE) taken from dogs treated with installed lidocaine (n=8) or serum physiologic (control, n=8). Samples were obtained at baseline and 3, 8, and 24 h following operation.*

Groups	Before operation (0.hr)	After operation		
		3.hr	8.hr	24.hr
Control	56.25 ± 12.95 ^{aA}	166.57 ± 25.39^{bA}	192.17 ± 24.62^{bA}	89.71 ± 16.10 ^{aA}
Lidocain	67.71 ± 6.98 ^{A}	82.60 ± 25.38 ^{B}	73.71 ± 9.75 ^{B}	76.00 ± 8.52 ^{A}

^{abc} means with different superscripts within one row differ significantly ($p < 0.05$)

^{ABC} Different letters in the column indicate the significant differences ($P< 0.05$)

Chapter 31

SUCCESSFUL TREATMENT OF CUTANEOUS SOLID TYPE ADENOCARCINOMA WITH CRYOSURGERY IN A PEKINGESE DOG

Murat KIBAR[1]

1 Artvin University, Artvin Vocational School, Department of Forestry, Hunting and Wild Life Programme, Artvin 08100, Turkey. Corresponding author: muratkibartr@yahoo.com

Introduction

Cryosurgery has been used for different benign, malignant, and premalignant dermis lesions by different practice methods, such as superficial spray, cotton-tipped applicator, intralesional, and cryoprobe (2, 5). When tissue is refrigerated, it is scarred by ice creation within the cells, vascular stasis and thrombosis, and the deliver of toxins and electrolytes. Extermination of malignant mass requires a resent tissue temperature of –60°C (3, 4).

Perianal glands in the dog are nonsecretory, altered sebaceous glands indwelled around the anus and predisposed to tumour (1, 7). The breeds most susceptible to perianal adenomas and carcinomas are the Siberian Husky, Cocker Spaniel, Pekingese and, for adenocarcinomas, the Bulldog and the Siberian Husky (6). The aim of this study is to defined the treatment of cutaneous solide type adenocarcinoma in a Pekingese dog through cryotherapy.

Case report

A 3.5-year-old, intact female Pekingese dog weighing 6 kg observed to have three different sized nodules on her perianal and vulva region for 2 months was referred to the small animal surgery clinic (Figure 1). Blood values were normal (Table 1). The first neoplasm localization was dorsal to the vulva and the others were bilateral to the vulva, ruby-coloured, of firm consistency, and of luminous mucosal appearance. The shape of the nodules were circular. The nodule diameters were 1.8, 1.5, and 1.2 cm. In cross section, the nodules were whitish-yellow in colour, of solid consistency, and characterized by thickening of the skin. The dog had not previously undergone surgical removal of tissue.

Criteria of selection were: no possible problem for the positioning of the cryoprobes, absence of articular involvement, planned cryoablation must cover the entire lesion volume, maximal diameter size of the tumor smaller than 2 cm, distance to neurovascular structures at least 3 mm.

The dog was premedicated with xylazine HCl (2 mg/kg, IM). The probe-based cryosurgical system (Üzümcü, Istanbul, Turkey) was used for cryoablation using a local anesthetic (Industrial Ave, Molendinar, Australia) as the interface for uniform freezing. This system was comprised of a tube of liquid nitrogen (-195 °C) and a probe (Figure 2). A probe with cryotherapeutic zones of 2 cm diameter was used in the study. The probe delivered liquid nitrogen, which did not come into contact with the ablated tissue. Being closed to liquid nitrogen flow allows for the thawing effect in the frozen cavity. Three cycles of freezing and thawing were induced, with the skin area being observed throughout (Figure 3). Freezing time was about 30 to 60 seconds. This was accomplished by ice creation over

the whole tumor with at minimum 5-mm of independent margins (Figure 4). Technical achievement was noted as an elongation of the ice ball going further the tumour margin and post-ablation views indicating no contrast rise in the field of the original tumor 6 months following the primary procedure. Postoperatively, the patient was administered intravenous antibiotics for 72 hr. No visible tumor was defined by day 45, and no recurrence was observed till 2 years.

The obtained nodular tissues was fixated in 10% of neutral formalin. The tissue was processed and established in paraffin wax. Edges 4-5 μm thick were cut from the block and mounted with entellan Neu (Merck, Darmstat, Germany). For histopathological examination, edges were painted with routine hemotaxylin and eosin.

This study describes the removal of 3 nodular adenocarcinoma in a patient who was successfully treated by cryoablation without complication. The histopathological examination showed that the layers of dermis and hypodermis were disturbed, and there was a bounded tumor nodule surrounded by massive fibrovascular stroma. Based on histopathological features, it was diagnosed as solid type perianal adenocarcinoma (Figure 5).

Discussion

The tumor varied from rosette, solid, to tubular types by histologically. The solid subtype consisted of sheets of neoplastic cells subdivided into thin bands of fibrous tissue, but lacked glandular structures (9). According the histopathological results, this case demonstrated characteristics of solid type adenocarcinoma with vast connective tissue, grid-type reticulation, and frequent mitosis. Tumor cells originated from the glandulocytes of the derma.

This type of tumor is most often seen in dogs between ages 5 and 14 (median 9 years) (9, 10). However, in this case, the dog was 3.5 years old; according the literature, affected dogs tend to be older. The breeds most susceptible to perianal adenomas are the Siberian Husky, Cocker Spaniel, Pekingese and, for adenocarcinomas, the Bulldog and Siberian Husky (6).

There are several great-scale studies display elevated therapy rates of cryosurgery for nonmelanocytic cancers of dermis (5). In the report by Kuflik (4), most cases were cured by curettage before use of the open spray technique, with a treatment rate of 99% in 522 cases. The 5-year therapy rate in squamous cell carcinoma lower than 2 cm (n = 134) was 100% (11).

Our reasearch is restricted to one case. However, cryoablation seems simple, suitable, and safe for advanced nodular tumors. All tumor masses ablateded after 2 cryoprobe treatments in the patient. Cryosurgery may

ensure long-term remission as integrate clinical alleviation was defined in the case till 2 years of follow-up. Also, the esthetic outcome was too extremely satisfactory. However, it should be determined that cryosurgery may not be acceptable for patients with tumors found in locations and conditions where cryosurgery is not useful, such as the eyelash region or medial canthus, to avoid damage of ocular tissue or canaliculus, acral part in patients with poor circulation or poor healing, or in locations where the nerves are quite outcrops, as this provides the potential risk of nerve wound. Moreover, cryosurgery is excellent to radiotherapy for its plainness, and as it is free of complications such as lymphedema, secondary cancer, and radiodermatitis (8).

In conclusion, cryosurgery can be an influental alternative cure for pleasent, nodular perianal cutaneous adenocarcinoma in animals, particularly those not suited for operation, or whose owners refuse to have them undergo operation Larger, controlled, and multi-disciplinary studies are required to approve its efficacy and safety.

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Table 1: *Dog's blood values.*

Datas	Values
WBC (/*l*)	11.3 10^9
Lymph (/*l*)	5.1 10^9
Gran (/*l*)	3.4 10^9
HGB (g/*l*)	172
HCT (%)	54.3
RBC (/*l*)	7.77 10^{12}
MCV (f*l*)	70.0
PLT (/*l*)	613 10^9

Figure 1: *View of nodules in perianal region.*

Figure 2: *View of criosurgery equipment.*

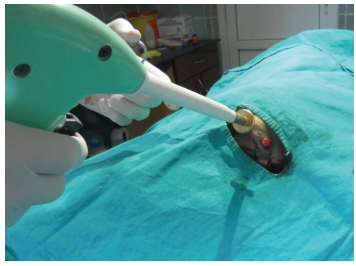


Figure 3: *Application of crioprobe to mass.*

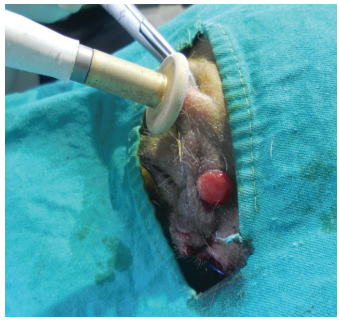


Figure 4: *View of the ice formation of the whole tumor.*

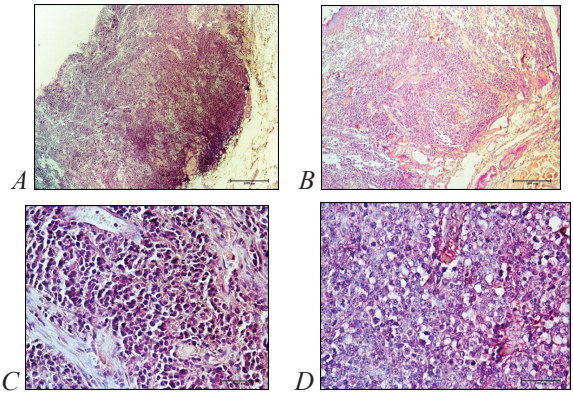
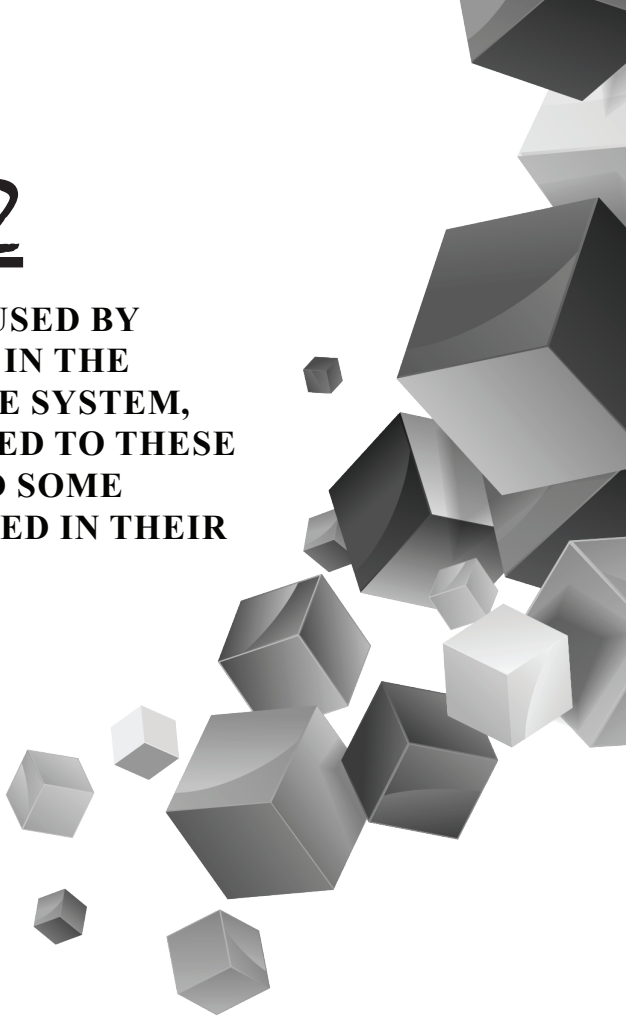


Figure 5: *Histopathological sections of circumanal nodules in female Pekingese dog. H&E. Barr=500 µm. (A) Epidermis, dermis and hypodermis structures destroyed. (B) Polymorphic, polyhedral cells organized in solid pattern and surrounded with massive connective tissue. (C, D) Tumour lobules observed well and they are separated with vast connective tissue. The lobes consist of the cells form solid sheets; have not abundant cytoplasm, quite pale, the nuclei are round with coarse chromatin and existence of one or more, but regular nucleoli. There is not a lot of aniscytosis, anisokaryosis and anisonuleoliosis and presence of frequent mitosis.*

Chapter 32

COMPLICATIONS CAUSED BY DIABETES MELLITUS IN THE MALE REPRODUCTIVE SYSTEM, MECHANISMS RELATED TO THESE COMPLICATIONS AND SOME CURRENT AGENTS USED IN THEIR TREATMENT



Dr. Öğr. Üyesi Saadet BELHAN[1]

Assistant Professor Saadet BELHAN[2]

1 Dr. Öğr. Üyesi Saadet BELHAN, Van Yüzüncü Yıl Üniversitesi Veteriner Fakültesi Dölerme ve Suni Tohumlama Anabilim Dalı, Van Türkiye

2 Assistant Professor Saadet BELHAN, Van Yuzuncu Yıl University, Faculty of Veterinary Medicine, Department of Reproduction and Artificial Insemination, Van, Turkey.

INTRODUCTION

Diabetes mellitus, which is a chronic and metabolic disease, has become alarming with its increasing incidence and complications (Dahlquist and Källén, 2005). It is known that diabetes is seen at a higher rate in men than in women (Schoeller et al., 2012). It progresses with hyperglycemia (Vlad and Popa, 2016). Prolonged hyperglycemia has been reported to cause excessive production of reactive oxygen species (ROS) (Baynes and Thorpe, 1999). Excessive amount of ROS causes DNA damage in sperm, impairment of sperm membrane functions and loss of fertility (Lopes et al., 1998). It has even been reported that excessively produced ROS can lead to apoptosis in germ cells (Jiang et al., 2014). It is reported that hyperglycemia in diabetes also causes neuropathy, cardiovascular disease, retinopathy, and nephropathy (Melendez-Ramirez et al., 2010). It is known that diabetic men experience a number of problems such as low libido, impotence, erectile dysfunction, ejaculation difficulties and infertility (Shi et al., 2017; Li et al., 2019). The impairment of the functions of leydig cells and a decrease in their number are shown as the cause of low libido (Foglia et al., 1969).

Testicular weight, testosterone level and sperm quantity are important parameters reflecting the reproductive functions of male animals (Ghanbari et al., 2015; Saumya and Basha 2016). In parallel with the decrease in leydig cells after diabetes, there is a decrease in testosterone synthesis (Foglia et al., 1969). Testosterone hormone plays a very important role in sperm production and maturation of the sperm (Haider, 2007). In the literature review, it was found that in diabetes, sperm quality deteriorated (sperm count, sperm motility and sperm vitality decreased while abnormal sperm count increased), reproductive hormone levels decreased, inflammatory marker levels (tumor necrosis factor α = TNF-α, interleukin-1β = IL-1β and interleukin-6 = IL-6 expression levels) and apoptotic marker levels (caspase 3, caspase 8, caspase 9) were found to increase (Adedara et al., 2019; Alsemeh et al., 2020; Ghosh et al., 2019; Jiang et al., 2020; Jiao et al., 2020; Khosravi et al., 2019; Nna et al., 2019).

In this section; the issue of diabetes, which reduces the quality of life of the patient by causing such problems in the male reproductive system, which has a very important place in the continuation of the generation, has been discussed. The purpose of the preparation of this chapter is to explain the complications that occur after diabetes in the male reproductive system, by which mechanisms these complications occur, and to summarize the healing effects of some current agents on these mechanisms.

Structures Primarily Affected in Diabetes

1) Sperm quality in diabetes

2) Testicular structure and functional status in diabetes

3) Hormonal balance in diabetes

4) Ejaculation and sexual function in diabetes

1) Sperm Quality in Diabetes

When many studies were examined, it was found that sperm count and motility decreased and abnormal sperm rate increased in diabetes (Adedara et al., 2019; Alsemeh et al., 2020; Jiang et al., 2020). Oxidative stress and decreased leydig cell function are thought to be effective in the problems caused by diabetes in sperm parameters (Ghosh et al., 2002). Testosterone is required for the normal course of spermatogenesis (Haider, 2007). However, the amount of testosterone decreases after hypogonadism in diabetes (Gianatti and Grossmann, 2020). After oxidative stress and a decrease in the amount of testosterone, sperm quality is expected to decrease.

2) Testicular Structure and Functional Status in Diabetes

Sperm count, testicular weight and testosterone amount are important parameters that reflect the reproductive capacity of the male (Ghanbari et al., 2015; Saumya and Basha, 2016). It is known that the histological structure of the epididymis is damaged and sperm passage is negatively affected in the diabetic condition (La Vignera et al., 2012). In experimental diabetes induced by streptozotocin, it has been reported that the morphology of the seminiferous tubules is disrupted and the number of sertoli and leydig cells decreases (Rashid and Sil, 2015). A recent study reported a decrease in the size of the Seminiferous tubules and the Johnson score, degeneration in spermatids, and a decrease in the protein levels of ZO-1, Occludin, Claudin-11 and N-cadherin in in the testicular tissue (Jiang et al., 2020). In another study, irregularity in the basement membranes of the seminiferous tubules, atrophy in the testicles, and degeneration in the spermatogenic cells were reported. It has also been reported that there is a decrease in the levels of testicular marker enzymes (asit fosfataz = ACP, laktat dehidrojenaz = LDH and γ-glutamil transferaz = γ-GT) (Jiao et al., 2020). Endothel cell swelling and germ cell shedding are also reported in the diabetic state (Sahu et al., 2020).

3) Hormonal Balance in Diabetes

Correct functioning of the Hypothalamic-Pituitary-Gonadal (HPG) axis is of great importance for a healthy reproduction (Condorelli et al., 2018). Hyperglycemia that continues for a long time in diabetes disrupts the function of the HPG axis (Steger and Rabe, 1997). The hypothalamus plays a key role in the hormonal mechanism of the male reproductive system (Murray et al., 1981). Again inhibin and Androgen Bindig Protein (ABP) also play a role in this mechanism (Ballester et al., 2004). Serum

testosterone concentration is negatively correlated with blood glucose level (Kim et al., 2014). Testosterone is of great importance in the regulation of spermatogenesis and in maintaining the physiological structure in the seminiferous tubules (Sharpe et al., 1992). With the decrease in testosterone, libido becomes distressed and sexual capacity is negatively affected (Ayuob et al., 2015). Indeed, it has been reported that penile erection and men's sexual desires depend on the concentration of testosterone in the blood (Jannini et al., 1999). Leydig cells are thought to be responsible for any malfunction in testosterone synthesis (Sharpe et al., 1992). It is known that the decrease in luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in diabetes may also cause problems in libido and spermatogenesis (Ayuob et al., 2015, Jangir and Jain, 2014). In a recent study, FSH, LH and testosterone levels were reported to be decreased in the diabetic group (Jiao et al., 2020).

4) Ejaculation and Sexual Function in Diabetes

Diabetic patients occasionally experience problems with ejaculation these problems; there may be early ejaculation, late ejaculation or retrograde ejaculation (Shamloul and Ghanem, 2013). The problems with ejaculation is thought to be caused by nerve damage in the penis (Ledda, 2000). Hyperglycemia that persists for a long time in diabetes; It may cause impairment in spermatogenesis and loss of sexual motivation (Bhattacharya et al., 2014; Khosravi et al., 2019).

The Main Mechanisms Involved in Diabetic Male Reproductive System Damage

1) Oxidative stress

2) Inflammation

3) Apoptosis

1) Oxidative Stress

Germ cells are vulnerable to ROS due to the excess of polyunsaturated fatty acids in their plasma membranes. It is known that oxidative stress plays an important role in the pathogenesis of diabetes and is effective in secondary complications of diabetes (Kanter et al., 2012). After hyperglycemia in diabetes; Oxidative stress begins as the formation of ROS increases and the antioxidant defense system is inhibited (Long et al., 2015). Over produced ROS damages the mitochondria of germ and leydig cells. This situation leads to impairment in spermatogenesis (Li et al., 2013). Studies have reported that the level of malondialdehyde (MDA) is high and the levels of catalase (CAT) and glutathione (GSH) are low in diabetic groups (Adedeji & Orisadiran, 2020; Ebokaiwe et al., 2020, Jiang et al., 2020). In another study, it was reported that superoxide

dismutase (SOD), glutathione peroxidase (GPx), CAT levels decreased and 8-hydroxy-2′ -deoxyguanosine (8-OHDG) levels increased in the diabetes group (Alsemeh et al., 2020).

2) Inflammation

It is known that proinflammatory cytokines have a role in the onset and progression of testicular dysfunction due to diabetes (Rashid and Sil, 2015). It has been reported that TNF-α, IL-1β, IL-6 levels were significantly increased in diabetic groups in many studies that created experimental diabetes (Adedara et al., 2019; Ghosh et al., 2019; Khosravi et al., 2019; Nna et al., 2019).

3) Apoptosis

Apoptosis that occurs under pathophysiological conditions is known simply as programmed cell death (Baron et al., 1994). Apoptotic cell death is among the complications of diabetes (Singh et al., 2012). Vimentin is one of the basic building blocks of the sertoli cells. After the collapse of the vimentin filaments, the spermatogenic cells are separated from the seminiferous epithelium and apoptosis occurs (Erkekoglu et al. 2012). Under normal conditions, testicular tissue protects sperm quality by eliminating abnormal germ cells in apoptosis. Excessive apoptosis, it may cause spermatogenic dysfunction by causing germ cell death (Adedara et al., 2015). In diabetes, overproduced ROS has been reported to induce apoptosis (Pácal et al., 2011). It is a known fact that the apoptotic index is also increased in diabetes (Alsemeh et al., 2020). Strontium fructose 1,6-diphosphate and apocynin have been reported to be effective in apoptosis after diabetes (Li et al., 2013; Tang et al., 2008). In a study conducted, it was reported that the application of Catalpol reduces Bax / B-cell lymphoma 2 (Bcl-2) levels in a dose-dependent manner and protects against GC-2 cell apoptosis caused by AGEs (Jiao et al., 2020). In many studies on diabetes, it has been reported that the expression levels of Bax, Caspase 3, caspase 8 and caspase 9 increase in diabetic groups (Adedara et al., 2019; Ghosh et al., 2019; Nna et al., 2019).

Some Current Agents Used in Diabetic Complications

In a study in which Salidroside isolated from Herba Cistanche was administered (25, 50, 100 mg / kg dose for 10 weeks); It has been reported that there is an increase in sperm quality, improvement in DNA damage, decrease in MDA and ROS contents, and increase in superoxide dismutase, catalase and glutathione activities. In addition, Salidroside has been reported to cause an increase in ZO-1, Ocludin, Claudin-11 and N-cadherin protein expressions, body weight and weight of reproductive organs (Jiang et al., 2020).

Nna et al. (2019) found that in the diabetic group, seminiferous tubule diameter and height decreased, germ cell loss increased, total antioxidant capacity and nuclear factor erythroid-2 related factor-2 (Nrf2) expression level decreased, and inducible nitric oxide synthase (iNOS), TNF-α and IL-1β expression levels increased. They also reported that the expression levels of Bax, Caspase 3, Caspase 8, and Caspase 9 increased and the expression level of Bcl-2 decreased. However, it is reported that Malaysia Propolis and Metformin administration alleviated testicular oxidative stress, inflammation and apoptosis.

In a recent study, catalpol was administered for 8 weeks in adult male rats of 14-15 weeks to investigate its effects on diabetes. It has been reported in the study that catalpol increases the level of reproductive hormones. It also inhibited oxidative stress-induced apoptosis and inflammation mediated by the advanced glycation endproducts (AGEs) / RAGE / NADPH oxidase type 4 (Nox4) signaling pathway. In summary, it has been reported to reduce male reproductive damage caused by diabetes by reducing apoptosis and inflammation caused by oxidative stress (Jiao et al., 2020).

Khosravi et al. (2019) reported that after administering diosgenin to diabetic rats, the level of MDA decreased, GSH, SOD, CAT and GPx activity increased, and TNF-α and IL-6 levels decreased. They also reported that apoptotic markers (Caspase 3, Annexin V and DNA fragmentation) decreased. In addition, they reported that diosgenin can improve sperm count, motility and vitality.

In another study, compared to the diabetes group, improvement in sperm parameters and histological structure of the testicles, a significant decrease in oxidative DNA damage and apoptotic index were reported in the group administered with hydroxytyrosol. In addition, an increase in body weight, testicular weight, androgen receptors and testosterone hormone has been reported. Again, a decrease in MDA level is among the reported information (Alsemeh et al., 2020).

Al-Roujeaie et al. (2017) created experimental diabetes with STZ (65 mg / kg) in their study. They started the routine application two weeks later and continued the treatment for 5 weeks (50 and 100 mg / kg dose). They reported that cGMP content in the penile tissue decreased, sexual functionality and sperm parameters improved, testicular damage was alleviated, inflammation and oxidative stress improved after the treatment.

In a study investigating the effects of black seed powder and thymoquinone on reproductive hormones in diabetic animals; STZ was administered to rats at a dose of 50 mg / kg and diabetes was induced. Testosterone levels were found to reach significantly normal values in diabetic groups treated with black seed powder and timoqinone (Aithal et al., 2016).

Feyli et al. (2017) investigated some effects of pentoxifylline in diabetic mice in their study. They applied pentoxifylline for 1 week starting 14 days after diabetes induction. They found that while the seminiferous tubule diameter, testicular weight, sperm parameters and testosterone hormone level increased significantly in the diabetic group treated with pentoxifylline compared to the diabetic group, the apoptosis index decreased.

Khamis et al. (2020) investigated the therapeutic effects of breast milk mesenchymal stem cells (Br-MSCs) at the molecular level in diabetic rats. They found that FSH, LH and testosterone levels, sperm count, motility and vitality were decreased in the diabetic group. They also found that proinflammatory and apoptotic markers and lipid peroxidation increased, and antioxidant activity decreased. After the administration of MSCs; They found that hypothalamic Kiss1, kiss1r, GnRH1, pituitary GnRHr and testicular kiss1r and PPAR-γ upregulated mRNA expression. They also reported that it increased FSH, LH and testosterone levels, antioxidant capacity and testicular proliferating cell nuclear antigen (PCNA) protein expression. In addition to these, they reported that it reduced lipid peroxidation and improved sperm quality. Finally, in the group treated with MSCs, reported that they detected a significant decrease in testicular NF-κB p65, TNFα, Bax, Fas, FasL, and Caspase 3, and an increase in Bcl2 mRNA expression and a low Bax / Bcl2 ratio.

Nanoparticles of *Loranthus micranthus* leaves, which are used by the public in Nigeria to lower blood sugar and treat infertility, have been used in diabetic rats and their effects have been investigated. When the group to which the nanoparticles of *Loranthus micranthus* leaves are applied is compared with the diabetic group; It has been reported that while SOD and CAT activities increase, MDA level decreases. In addition, it has been reported that activity of myeloperoxidase (MPO) and TNF-α level decrease, LH, FSH, prolactin and testosterone levels increase and sperm parameters improve.

CONCLUSION

Diabetes mellitus, which is an important health problem of today and the future with its many complications, which negatively affects the quality of life of patients, its increasing incidence and its occurrence in men of reproductive age are worrying for the future. Continuous studies are carried out to minimize complications in diabetic patients. However, unfortunately, a fully determined prescription has not been reached yet.

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Chapter 33

MAXILLOFACIAL TRAUMAS

Uzm. Dr. Muhammet DILBER[1]

1 Dilber ENT& Aestetic Clinic, Istanbul E-mail: muhammetdilber@hotmail.com

1. INTRODUCTION

Maxillofacial traumas (MFT) are the traumas involving head and neck injuries other than the cranium and overlying hairy scalp. The injuries in this area include; skin and underlying soft tissues, skeletal structure, paranasal sinuses, nose, orbit, oral cavity, lower jaw and teeth, directly or indirectly.

A large portion (80%) of the trauma cases that refer to the emergency departments consist of facial area injuries with head, face and neck injury complaints. There may be many factors in its etiology. These can be; sports injuries, motor vehicle accidents, gunshot wounds, alongside assault and domestic violence. In developing countries such as our country, among MFT causes, the first is traffic accidents (60%) (Başer E, 2019). The situation is slightly different in developed countries; while traffic accidents are the second most frequent case, the first is assault (41%).

Maxillofacial traumas bring cosmetic losses alongside problems that have vital significance for patients. The most important one of these vital problems is airway obstruction, while another vital problem is serious bleeding that can occur in the branches of the external carotid artery after middle face and mandibula injuries (Bagheri et al., 2006; Eckstein, Chan, Schneir, & Palmer, 2000). Most of the maxillofacial trauma cases consist of men between the ages of 20-40, and the most important etiological cause is trauma (Gassner, Tuli, Hächl, Rudisch, & Ulmer, 2003; Ozgursoy, Muderris, Yorulmaz, & Kucuk, 2009).

In cases with fracture in the facial bones, having cranial, thoracal and abdominal injuries and extremity fractures alongside it increases risk. In the study where they evaluated 151 maxillofacial trauma cases, Alvi et. al. detected cerebral hematoma damage in 43.7% of the cases and pulmonary damage in 31.1% of them. The morbidity and mortality of these cases are much higher (Alvi, Doherty, & Lewen, 2003). From this point of view, considering the possibility of multiple traumas in maxillofacial trauma cases, it should be evaluated with a multidisciplinary approach from different branches such as brain surgery, eye diseases, plastic surgery and jaw surgery.

2. GENERAL APPROACH

The first and foremost priority after maxillofacial trauma is to ensure the patient's airway patency. During first and emergency response, difficult airway management, intubation or ensuring airway patency with tracheotomy should be planned in cases with maxillofacial trauma (Lockey et al., 2015; Stiell et al., 2008).

The primary aim after trauma should be; to stabilize vital functions early, and electively fix functional and cosmetic problems later.

After the vital functions of the cases have been stabilized and the situations that require immediate intervention such as the airways have been determined and the necessary procedures have been performed regarding them, the case should be subjected to a second, more detailed evaluation; the functional and cosmetic problems should be determined. In cases with heavy bleeding, the bleeding focus should be determined and the required emergency responses should be made. The entirety of the patient's face area should be evaluated in detail as a whole, foreign objects, hematomas that may interfere with the evaluation should be cleaned. The necessary radiological tests should be performed in cases suspected to have fractures in the facial bones.

After the situations that require emergency responses are eliminated and a detailed physical examination and the necessary imaging tests are done, the patient should be evaluated together with their anamnesis. At the end of all the evaluations, in cases limited to soft tissue trauma, suturing should be performed if necessary, as for the cases with fractures detected in the facial bones, the timing and immediacy of the intervention regarding the fracture should be planned.

3. IMAGING

The main purpose of imaging after trauma is to accurately present the location, number of the fractures and damage they caused. After the damage detection, radiological detection plays a key role in protecting the function of the tissues, preventing potential complications and cosmetic problems (Mehta, Butala, & Bernstein, 2012). While reviewing MFT traumas, knowing the damage that occurred in the soft tissues, the functional losses caused by the fractures in the bone structures, and preparing the radiology reports taking this into consideration will increase success rates in the stages after diagnosis.

Currently, computerized tomography sustains its validity as the golden standard method in evaluating maxillofacial trauma cases. Certainly, other imaging methods (MRG, USG etc.) are also quite useful in guiding the diagnosis, according to the state of the patient.

Although direct radiographs that are low cost and have lower amounts of radiation compared to tomography can be used, due to the disadvantages of direct radiographs (superposition, failure to always provide the desired and sufficient amount of detailed examination etc.), its usage is limited in cases with maxillofacial trauma. Routine radiographic films used in evaluating face injuries include, Waters x-ray, Caldwell x-ray and lateral facial x-ray. Caldwell x-rays, by displaying the orbit and posterior facial structures well, can be used together with Waters x-rays in diagnosing middle face fractures. Especially by using high resolution tomography, it can evaluate even the smallest facial bone fractures and with the 3-dimensional arrangement of the images, it is quite a guide in diagnosis and planning treatment.

4. ZYGOMATICOMAXILLARY COMPLEX FRACTURES

The zygomatic bone creates a joint with the frontal, maxillary, temporal sphenoid bones. Due to this structure, the zygomatic bone forms the corner points of the lateral part of the face. Simultaneously, the zygomatic bone is also located in the area where the lateral maxillary and upper transvers maxillary bones join. Due to this placement, we can encounter zygomaticomaxillary complex fractures as mono-, di-, tripod.

Visual impairment finding and hearing loss can occur in zygomatic bone fractures. Again, a delay in the timing of the treatment for the zygomatic bone displaced fractures, can create enophthalmos, sequelae due to compression in ocular muscles and related limitation in movement, and cosmetic deformities. In the diagnosis of zygomatic fractures, after the physical examination, direct radiographs and tomographic examinations (face CT) are required in order to display the spread of the injury (Image 1) (Mehta et al., 2012).

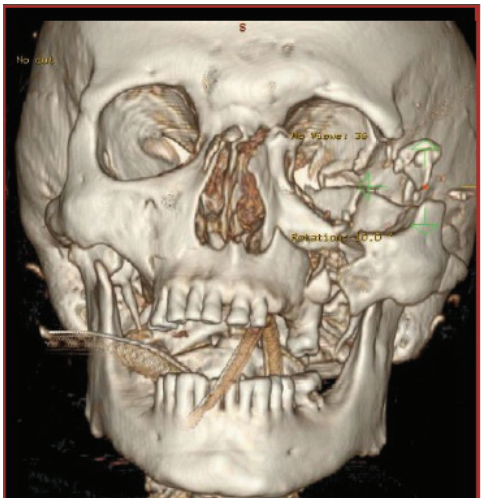

Image 1. A Facial Computerized Tomography that shows zygomaticomaxillary complex and tripod fracture with three-dimensional reconstruction

The purpose of zygomaticomaxillary complex fracture treatment is to; reduce the fracture in zygomatic-frontal, zygomatic-maxillary and infraorbital rim axes and provide sufficient correction. The possibility of accompanying orbital base fractures in fractures of this area should be thought of and taken into consideration while planning the treatment.

The maxilla is placed in the midline of the facial skeleton and significantly contributes to the formation of the vertical plane of the face and the upper jaw. In middle face area trauma and fractures, due to their close vicinity, after the trauma the patient can have; malocclusion, resistant epistaxis, smell and taste deficiencies, tear duct blockages and cosmetic deformities.

Maxilla fractures have been classified into three groups and examined by Rene Le Fort (Le FOrt, 1901). According to the Le Fort classification;

1. **Le Fort I (Floating Palate) (Horizontal Maxillary Fracture)**

Occurs secondarily with blunt trauma to the lower 1/3 of the middle face. The fracture line runs towards the maxillary sinus from the maxillary alveoli piriform aperture. Depending on the fracture that occurred, it results in separation of the hard palate or maxillary alveoli from the skull base.

In the patient; edema in the face and upper lip, ecchymosis in the buccal vestibule and labial, pain while chewing-talking and biting and in relation to this, movement limitation, malocclusion and downwards displacement of the upper jaw and mobility in the upper jaw is observed in the examination.

2. **Le Fort II**

Develops related to blunt trauma to the midline of the middle face. The fracture line separates the pyramidal structure including the maxilla hard palate, dental arch and teeth, from the upper craniofacial area in the roof, the inferior orbital rim and nasofrontal junction level in the base. The maxilla and root of the nose are felt as mobile during examination.

In the patient, findings such as the hard palate and nose being palpated as mobile, bilateral periorbital edema and ecchymosis, edema in the middle face area and malocclusion are encountered. In cases with a Le Fort fracture, coronal and axial sectioned facial CT scan with three dimensional reconstruction shows these complex injuries in the best way (see Image 2) (Mehta et. al., 2012).

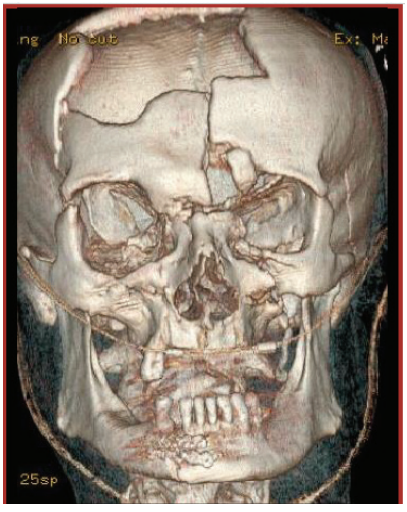

Image 2. Facial Computerized Tomography with three-dimensional reconstruction showing double sided Le Fort II in a patient who has a fracture including the face

3. Le Fort III

Develops secondarily to blunt trauma to the upper part of the middle face area. The fracture line reaches the other eye by going through the zygomatic-frontal area, orbital lateral wall and nasofrontal junction. During the examination with palpation, total mobility of the maxilla is detected. This finding is called the drawer sign. The presence of a drawer sign means that there is separation in the whole face.

In the patient; bilateral subconjunctival bleeding, ecchymosis in the shape of glasses around the bilateral eye (racoon eye finding), important airway obstructions with the increase of intercanthal distance can be seen.

The treatment planning of Le Fort fractures should be done with an approach appropriate to the classification. In Le Fort I fractures, fracture lines in the maxilla medial and lateral are fixed to the upper structures. In Le Fort II fractures, correction is applied to the medial maxillary and infraorbital margin. In Le Fort III fractures, injuries in nasal cavities, orbit base and maxillary sinus areas must be fixed as well, alongside the correction of bone structures. The point to pay attention to in the correction is that there is no malocclusion.

5. MANDIBULA FRACTURES

Due to the mandibula having two pieces on an anatomically horizontal and vertical plane located on the anterior and lateral of the face, it is in a quite open position to traumas towards the middle face area. Although it is structurally one of the hardest bones of the face, in isolated bone fractures, it is in second place after the nasal bones (Erdmann et al., 2008; Kelley, Crawford, Higuera, & Hollier, 2005). The anatomical and functional relationship of mandibula with the oral cavity increases the importance of fractures in this area. Patients that have mandibula fractures can have impairments in functions such as speech, eating and drinking, chewing due to the restrictions in mouth movements and additionally the flora here has a high risk of causing wound infections due to its relationship with the oral cavity.

The relatively weak and more vulnerable points to trauma of the mandibula can be compiled as the Symphysis/Parasymphysis, Angulus and Subcondylar area. Depending on the effect size of the trauma and its location, the fracture can occur directly at that point or also in different and weaker points through energy transfer due to trauma.

In cases with a mandibula fracture present, lacerations on the skin or edema, hematoma, ecchymosis, mucosal tearing in the oral cavity can be observed. In these cases, after a careful inspection, the jaw movements and the presence of crepitation should be checked with mandibula palpation. Also, temporomandibular joint dislocations should be carefully examined.

In cases with a mandibula fracture, collectively reviewing the symptomatology and findings that can be obtained from the examination, these are; pain and trismus, limitations in mouth opening, presence of crepitation and/or physical deformity, occlusion disorders, biting difficulty, paralysis of the lips-loss of sense, gingival ecchymosis, asymmetry and numbness in the face.

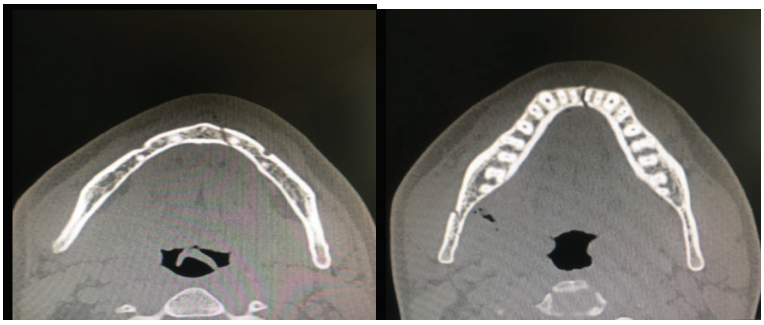

Image: A patient with a mandibula fracture at our clinic

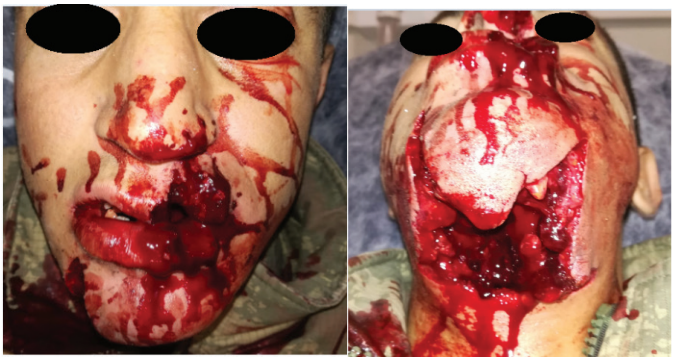

Image 3-4: A young male case from our own clinic who developed wounds in the skin, soft tissues, muscle tissues, base of the mouth and deformities after a gunshot injury, who also has a mandibula fracture.

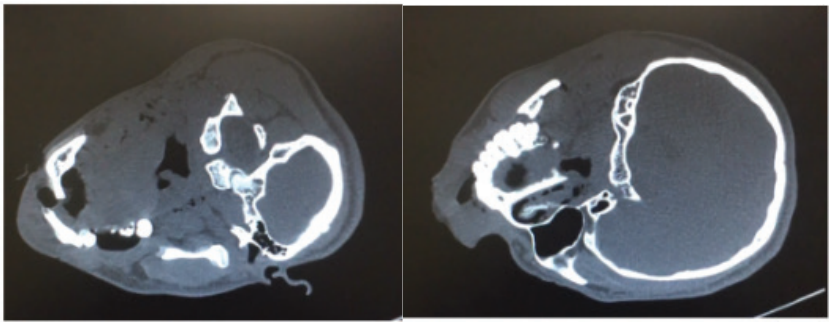

Image 5-6: Computerizes tomography sections of the case

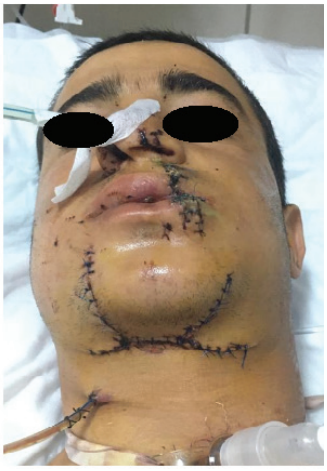

Image 7; The post-op image of the case (the necessary soft tissue, mouth base and muscle tissue reconstruction was provided, the mandibula fracture was reduced with plaque-screw, airway safety was ensured with tracheotomy.)

In the treatment approach of mandibula fractures, firstly, in the case that the patient is not in a life-threatening situation and there is no problem about their airways, planning should be made. In general, in the first phase of the treatment approach, wound cleaning, oral antisepsis, intravenous antibiotherapy and tetanus immunization should not be forgotten. After these steps, reduction should be planned considering the anatomical placement of the fracture, the functional impairment it caused and reversing the cosmetic defect.

Points and reduction methods that should be paid attention to in the reduction of mandibula fractures: (Ellis III, Muniz, & Anand, 2003; Ferreira et al., 2005; Mijiti et al., 2014; Murray, 2013; Vartanian & Alvi, 2000);

1. Ensuring the necessary aseptic conditions in the reduction process to avoid infection,

2. Planning the reduction to be in the position to provide the right occlusion,

3. Joining the fractured ends and/or parts on the right anatomical plane and fastening them,

4. Ensuring detection throughout the bone healing period with the suitable and correct reduction method

5. Reduction Methods:

- Closed-External Methods

- Bandages
- Interdental wiring and arch bar application
- Intermaxillary fixation
- Open-Internal Methods
- Open reduction and intermaxillary fixation
- Open internal and external fixation

Points that should be paid attention to for a successful open reduction in mandibula fractures, especially internal fixation; applying anatomical reduction, ensuring functional stabilization, using an atraumatic surgery technique and starting the active physiological functions quickly and as early as possible. Currently, many differently materials have been produced to be used in this area. These are;

- Micromini plaques

Plaques with a screw diameter of 1.0-1.5 mm. Their usage in mandibula fractures is limited.

- Mini plaques

Plaques with a screw diameter of 2.0 mm. They are the ideal plaques most frequently used in fixing mandibula fractures.

- Compression plaques

They provide positive contributions to bone healing by creating compression between both fracture lines. Their usage in mandibula fractures are limited.

- Lag screw fixation

It can provide osteosynthesis in mandibular fractures. It can be applied effectively especially in oblique fractures.

- Bioabsorbable plaques

They do not have routine usage in mandibula fractures. They are thought to be used in pediatric cases.

The most important complications that may develop in mandibula fractures;

- Malocclusion

Develops due to the insufficient reduction of the fractured pieces or their insufficient stabilization. Insufficient bone support, especially in partial fractures, increases malocclusion risk.

- Infection

The presence of partial fractures, presence common mucosal destruction, the application of a traumatic surgical attempt, insufficient fixation and the patient having comorbid diseases that may create a tendency for infection increases its risk.

- Nerve Damage

The most commonly affected nerves in this area are the inferior alveolar nerves and mental nerves. The pre-op evaluation of the nerve damage being related to the trauma or not is quite important.

6. FRONTAL BONE FRACTURES

Due to its resistant and thick cortical structure, the frontal bone is the bone most resistant to trauma in the skull skeleton. Thus, for frontal bone fractures to occur, it must be subjected to high intensity trauma. As a result of high intensity traumas, the possibility of frontal bone fractures showing associations with intracranial pathologies and other area fractures are high. While the most frequent etiological cause of frontal bone fractures is motor vehicle accidents, currently a proportional increase with other etiological causes is also present. The reason for this is estimated to be the strictly enforced traffic rules today.

Frontal sinus fractures comprise 5% to 15% of maxillofacial fractures (Bell, Dierks, Brar, Potter, & Potter, 2007). Frontal sinus fractures are generally classified with the front wall or back wall involvement. Additionally, both wall fractures can be partial or non-partial, displaced or non-displaced. Again, in the evaluation of the fractures in this area; the involvement of the nasofrontal canal or anterior cranial fossa dura has importance.

Deformities, deep lacerations, dents that are felt in palpation, cosmetic defects and intracranial incidents in the frontal area, while can be symptoms of fractions in this area, detecting clear colored rhinorrhea should suggest that there is dura damage accompanying the frontal sinus fracture. Also, in cases where a delay in treatment timing occurred, intracranial infections can ensue.

Cranial imaging has great significance in the diagnosis of frontal sinus fractures, and in suspected cases, taking a brain CT maintains its place as a significant and preferred test in evaluating anterior and posterior tabulae and evaluating pathologies belonging to intracranial structures. (Image 45.1)

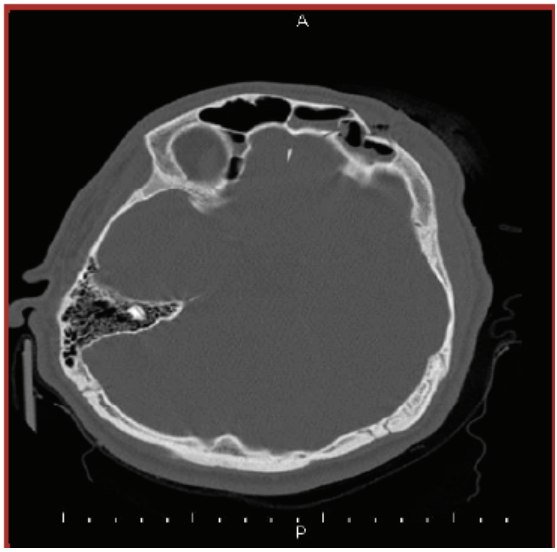

Image 45.1: Frontal Sinus Fracture CT Image

In the treatment of strong frontal sinus fractures, the anatomical structures that must be evaluated have been discussed in five groups (Strong, 2008)

- Anterior wall fracture
- Posterior wall fractures
- Nasofrontal canal fractures
- Dura damage
- Partial fractures

The primary and fundamental aims in the treatment approach of frontal sinus fractures (Ioannides, Freihofer, & Friens, 1993; Kalavrezos, 2004);

- If any, dura damage repair,
- Prevention/treatment of the early and late complications in the central nervous system
- Ensuring the functions of the frontal sinus and nasofrontal canal
- Correcting the cosmetic deformities in the frontal area

The main methods used in the treatment of frontal sinus fractures;

- Monitoring
- Repair with endoscopy aid

- Open reduction and internal fixation
- Frontal sinus obliteration
- Cranialization

When choosing a repair method for frontal bone fractures; the displacement of the anterior/posterior wall, dura damage or brain cerebrospinal fluid leakage, the presence of nasofrontal canal damage are determiners.

Again, for patients that are suspected of frontal sinus fractures, starting the necessary and sufficient antibiotherapy including sinus pathogens early plays an important role in preventing potential infective complications.

7. ORBITAL FRACTURES

The orbital bone roof consists of seven different bones;

- The lateral wall consists of the zygomatic bone and the greater wing of the sphenoid bone,
- The medial wall consists of the maxillary, ethmoid, lacrimal and sphenoid bones
- The surface consists of the frontal piece of the maxilla, zygomatic and palatine bones
- The ceiling consists of the orbital piece of the frontal bone and the lesser wing of the sphenoid bone

There are two main orbital fracture types;

The first type includes one or more fractures than the orbital bone walls. Especially the inferior orbital rim breaks frequently and relocates towards the inside of the orbit. This fracture frequently affects the more sensitive areas of the orbit and causes secondary fractures.

The second type of orbital fractures is, with its common name, orbital blow-out fractures. This type occurs when a small-diameter object hits the eyeball and causes an orbital wall fracture without causing an orbital rim fracture. The vicinity fat tissue and extraocular muscles can get stuck in the maxillary or ethmoid sinus after the trauma.

Today, orbital and/or facial computerized tomography scanning, alongside providing quick and detailed information on the size of the orbital fracture, its location and related soft tissues, is the golden standard imaging method to investigate other accompanying injuries. (Image 45.3)

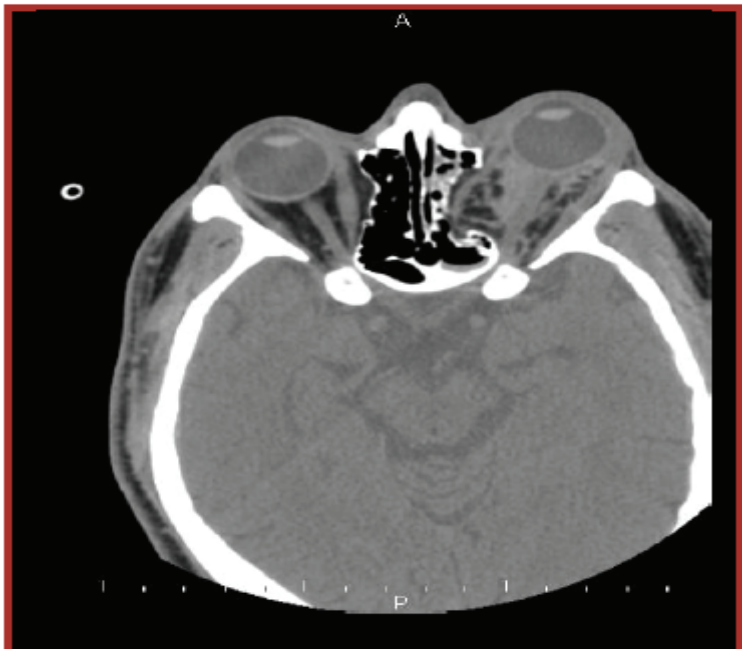

Image 45.3 Medial Wall Deformity Occurring After a Left Blow Out Fracture in a Facial CT Section

In a patient who is suspected for an orbital fracture, all orbit sides should be carefully palpated for any deformities. In orbital fracture cases, numerous physical examination findings can ensue. Periorbital ecchymosis, ptosis, hypertelorism, enophthalmos, exophthalmos, bleeding, asymmetry in the face can be some of the symptoms that can be observed.

During the first examination of cases who are suspected for an orbital fracture, after situations that can lead to vital risks have been eliminated, conducting the 5-point ocular evaluation suggested by Gossman et. al. is important and functional (Gossman, Roberts, & Barr, 1992). In this examination; visual acuity, pupillary reactivity, anterior chamber, posterior chamber and extraocular muscle functions are evaluated.

In patients with only an orbital fracture, the necessary antibiotherapy for the sinus pathogens should be started until treatment for the fracture is applied. Currently, a consensus has been reached on the delayed treatment of orbit fractures is the ideal application in many situations (Matteini, Renzi, Becelli, Belli, & Iannetti, 2004). Although intervention can be delayed until one or two weeks in adults, earlier repair should be done in child patients. Urgent eye consultation is also necessary for accompanying eye injuries.

Retrobulbar hematoma or malign orbital emphysema can lead to ocular compartment syndrome and with exophthalmos, findings such as decreased visual acuity can be encountered. In this case, some emergency responses should be planned to reduce inner eye pressure and ischemia. Orbital fissure syndrome may develop in orbital fractures accompanied by injuries in the ophthalmic branches of oculomotor nerve and trigeminal nerve. In extraocular movements, paralysis, ptosis and periorbital anesthesia can be named among findings that point to orbital fissure syndrome. Again, in orbital fractures, orbital apex syndrome may occur as a result of the orbital nerve being damaged as well and reduced visual acuity can be seen in the patient.

8. NASO-ORBITO-ETHMOID COMPLEX FRACTURES

The naso-orbito-ethmoid area is located in the center of the middle face and is in the close vicinity of vital structures such as the eyes, skull base, frontal sinuses. While the anterior of the naso-orbito-ethmoid area consists of structures relatively more resistance to trauma such as the frontal, maxillary and nasal bones, its posterior is made of relatively flimsier structures such as the ethmoid bone. The fractures in this area occur especially after traffic accidents, intense hits to the face and falls. The fractures in the naso-orbito-ethmoid generally accompany other bone fractures in the face.

Naso-orbito-ethmoid complex fractures are evaluated according to the classification made by Markowitz and Manson (Markowitz & Manson, 1989). According to this classification;

- Type 1: En bloc fracture with the dislocation of the central bone piece

  Tip 1a: Moderate level fractures

  Tip 1b: Wide sized fractures

- Type 2: Partial naso-orbito-ethmoid complex fractures in which the central connection of the medial canthal ligament is preserved

- Type 3: Partial naso-orbito-ethmoid complex fractures in which the central connection of the medial canthal ligament is separated

The most fundamental characteristic that separates naso-orbito-ethmoid complex fractures from isolated nasal fractures is that alongside a nasal fracture, there is also a fracture in the medial maxillary and/or upper maxillary bone support and this fracture can show proceed in different directions along the ethmoid bone. Physical examination findings also vary depending on which part or parts of the ethmoid bone, which has a thin lamellar structure, is damaged. In fractures that extend towards the anterior skull base, hyposmia, anosmia, rhinorrhea, defects in the skull base; in fractures around the nasofrontal reses, recurrent frontal rhinosinusitis,

mucosal; in fractures around the nasolacrimal canal, dacryocystitis, dacryocystocele; in fractures around the orbit, enophthalmos, telecanthus and orbital dystopia can be observed. Furthermore, in cases that bilateral periorbital ecchymosis is detected (with its common name, racoon eyes finding), anterior skull base defect should be suspected.

The repair of naso-orbito-ethmoid complex fractures is quite difficult and it requires many areas to be evaluated together. Before surgical planning, the presence of especially damage to the skull base and/or medial canthus damage should be determined. It is very important to differentiate epistaxis and rhinorrhea after trauma. The most objective test method for this differentiation is to look at beta 2 transferrin in the fluid taken from the nose. However, the laboratory examination taking a few days is the most basic limitation of this test. The "halo test", which is relatively subjective, can also be applied in the detection of rhinorrhea. In this test, the fluid taken from the nasal cavity is dropped onto a white paper and the presence of a clear halo around the bloody appearance means high suspicion for rhinorrhea.

The main aims in the treatment of naso-orbito-ethmoid area fractures;

- Repairing of skull base defects and if any, the accompanying brain cerebrospinal fluid leakage
- Fixing the intercanthal distance
- Mending the nasal contour and projection back to normal
- Repairing the soft tissue damage around the nose and eyes.

The open technique is generally preferred in the repair of naso-orbito-ethmoidal complex fractures. This way, the field of view is widened and it is possible to fasten with a plaque or a wire.

9. FACIAL TRAUMA

Facial area trauma is mostly not life threatening but should be discussed as a whole. Firstly, the airways must be taken under control. Potential dangers for airways can be named as; fractured teeth and the presence of foreign objects, multiple fractures, avulsed tissues, tongue edema, direct trauma to the larynx or trachea da trauma.

Facial area trauma is generally investigated in two ways; soft tissue injuries and bone fractures-dislocations (Image 1-2). The patient's face should be evaluated in different angles in a controlled manner. The presence of structural asymmetry, lacerations, abrasions, contusions, avulsions or hematoma in all of the head and neck area, especially the face area, should be examined. The sensitivity, dents, crepitations of the facial bones should be evaluated with palpations. Palpations for the bones can be made from

inside the from in situations where it cannot be distinguished due to edema. The functions of the VII. head pair (facial nerve) that ensures the motor and sense innervation of the face and the V. head pair (trigeminal nerve) should be evaluated in the nerve examination. Investigating the mobility or the presence of crepitation by palpating through the maxilla anterior alveolus to reveal the middle face fractures is quite beneficial. In addition, the mandibula should be palpated, temporomandibular joint cavity and jaw movements should be evaluated. All of the teeth should be checked, fractured or missing teeth should be looked at, whether there is a problem in closing it should be investigated during intraoral examination. If there are teeth that were lost in the mouth, lung imaging should be done considering the risk of aspiration.

As for the treatment approach of facial area trauma, primarily, in the case that the patient does not have a life-threatening situation and has no problems with their airways, planning should be done. Generally, in the first phase of the treatment approach, wound cleaning, oral antisepsis, appropriate antibiotherapy and tetanus immunization should be done. After these steps, the appropriate treatment plan according to the trauma results of the structures in the related area should be started without wasting time. The treatment should be planned in order to reverse the functional dysfunctions and cosmetic defects that resulted from soft tissue injuries or anatomical fractures.

CONCLUSION

Since the neck and upper respiratory tracts that are vital for life, are within the trauma area of the facial area, the diagnosis and treatment of the emergencies in this area must be done quickly.

MFT can cause results alongside mortality, including serious functional losses and cosmetic deformities. After getting the airways under control in these patients, treatment should be planned without wasting any time in order to minimize morbidity.

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Chapter 34

LONG-NONCODING RNAS AND BREAST CANCER

Prof. Dr. Berna TAN[1]

1 *İstanbul Medeniyet Üniversitesi, Tıp Fakültesi, Temel Tıp Bilimleri* E-mail: brndemircan@hotmail.com

Introduction

Breast cancer is the most prevalent malignancy and represents the most common cause of cancer mortality among females worldwide (1). The high incidence and also death numbers are linked to diverse mechanisms such as heterogenous nature of the disease, distant metastasis and drug resistance (1-3). Heterogeneity is displayed intertumorally and intratumorally, and also affects one anatomic site of the breast in terms of phenotypic and molecular diversity (2). Breast cancers originating from ducts and lobules are called ductal and lobular carcinoma, respectively. Ductal carcinomas comprise the most of the cases. Breast tumors are usually classified into ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC). DCIS is a noninvasive, early breast lesion and characterized by proliferation of abnormal epithelial cells contained within the ducts, while IDC has the cells with invasive capacity that spread beyond the duct. If precursor lesions of breast would arise from the lobules, it then progresses to invasive lobular carcinoma (4,5).

Previously, clinical subtyping of the breast tumors were based on hormonal receptor status of estrogen receptors (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). However, thanks to advances in molecular assays, breast cancers are classified in five subtypes according to profiling of gene expression: Luminal A, Luminal B, basal-like or triple-negative, normal-like and HER-2 type (1,2). Luminal A tumors exhibit positive ER and PR expression and negative HER2 expression. Luminal B breast tumors have positive ER and PR, positive or negative HER2 expression. HER2 breast cancers display positive HER2 expression but negative ER and PR expression. The normal-like subtype contains tumors expressing ER and PR are HER2 negative. Triple-negative breast cancers (TNBC) are negative for ER, PR and HER2, and this type of breast cancer are the most aggressive subtype (1).

All these mentioned subtypes are involved in distinct survival rate and response to therapies. Luminal A and B tumors respond well to hormone therapy and usually have better prognosis, however Luminal B tumors have worse prognosis in comparison to Luminal A subtype. HER2 tumors are treated with targeted therapies like HER2 monoclonal antibodies. Despite the sensitivity to targeted therapies, HER2 tumors are involved in poor prognosis due to the risk of early relapse. Since TNBC patients lack of ER, PR and HER2, they cannot have treatment of endocrine or HER2-targeted approaches (1,2). It has been reported that TNBC patients indicate a higher degree of distant metastasis, a poor clinical outcome and decreased disease-free and overall survival as compared to patients with other subtypes of breast cancers (1).

Although there have been numerous developments for the purposes of diagnosis and therapy, a high incidence of mortality because of

metastasis and drug resistance still continue to be a challange in breast cancer. Comprehensive understanding of molecular basis of breast cancer is important to develop new biomarkers and potential therapeutics. Genetic mutations as well as epigenetic modifications play major roles in initiation, progression, metastasis and drug resistance of breast cancer (6). Noncoding RNAs (NcRNAs) are one of the important epigenetic mechanisms that regulate gene expression. They can modulate various cellular processes such as chromatin remodelling, transcription, post-transcriptional modifications, and also regulate some signal transduction network through having wide range of simultaneous targets. Hence, ncRNAs play key roles in diverse pathological conditions including breast cancer (7).

Based on their length, ncRNAs are divided into two categories; short ncRNAs which is smaller than 200 nucleotides in size, and long ncRNAs (lncRNAs) (≥ 200 nucleotides in size) (1,2). LncRNAs and their functions in breast cancer will be main focus of this chapter.

Biogenesis and Action Mechanism of Long-Noncoding RNAs

Until the past decade, lncRNAs which lack of coding potential was regarded to be 'junk' transcriptional products or 'transcriptional noise' of the human genome. However, current research has highlighted their crucial role in different physiological and disease conditions (7). LncRNAs perform a profound actions on the regulation cellular growth, tumor microenvironment, epithelial to mesenchymal transition (EMT), angiogeneis, metastasis by numerous mechanisms (8). LncRNAs are divided into six classes according to their gene loci and orientation;

1. Intergenic lncRNAs originating from DNA sequneces between two genes,

2. Intronic lncRNAs produced by introns of protein-coding genes,

3. Overlapping sense lncRNAs, which overlap with open reading frame for one or more introns and exons of different genes,

4.Antisense lncRNAs which are also called natural antisense transcript are originated from an opposite direction to a coding gene,

5. Enhancer lncRNAs are produced by promoter enhancer

6. Bidirectional lncRNAs starting from proximity of a coding transcript of the opposite strand (3,9).

A distinct category of lncRNAs are the circular RNAs (ciRNAs) which are abundantly expressed in mammals. CiRNAs are highly conserved and consist of a single stranded circular RNA including hundred to thousands of nucleotides in size. They are produced via backsplicing events resulting in circularization of their 3' and 5' ends through covalent bonds (1,8).

Deep and sensitive RNA sequencing methods demonstrated the number of lncRNAs have been arising continuously. Encyclopedia of DNA Elements (ENCODE) Project Consortium reported that greater than 120.000 different lncRNA transcript were encoded by human genome and most of them are still not characterized (7).

The genes of lncRNAs are transcribed by RNA polymerase II and do not encode for proteins. Most of lncRNAs are exposed to 5'capping, splicing, 3'cleavage and poly-adenylation (1,2,7). Loci of lncRNAs are identical with the protein-coding genes at chromatin level, but they generally do not contain introns. As in the case of pre-mRNAs, lncRNAs experience maturation by splicing. LncRNAs are generally localized in the nucleus, however they are also available in the cytosol and exosomes (1). It has been demonstrated that lncRNAs have lower expression levels relatively to protein-coding genes, and also pattern of their expression is specific for cell type (1,7). As compared to protein-coding gene, lncRNAs have been indicated to be exposed to low selective pressure, yet genomic repeat sequences have lower selective pressure than that of lncRNAs. The structure and cellular localization of lncRNAs have been protected during evolution since it is certain to detect short quite conserved sequences when compared the lncRNAs' sequences in diverse species (1).

LncRNAs have generally stem-loop secondary structures and they use a wide range of mechanisms to regulate the expression of genes affecting various biological functions (7). Despite not fully understood of majority of them, action mechanisms of lncRNAs fall into five classes.

a. *Chromatin remodelling*; lncRNAs may increase or repress transcriptonal activity by stabilizing open/closed chromatin. They perform the function as *cis* or *trans* fashion, and *cis* interacton consists of transcriptional activation or suppression of target genes. On the other hand, *trans* lncRNA chromatin interaction includes the control of co-expressed genes through binding chromatin-modifying complexes.

b. *Scaffold for RNAs and proteins;* lncRNAs act as scaffold, thus associate with nucleic acids by their sequence complementarity and proteins via their structural RNA elements

c. *Sequestering miRNAs, mRNA and proteins;* lncRNAs called as competing endogenous RNAs (ceRNAs) have been indicated to regulate the expression by functioning as miRNA sponges, hence inducing the target mRNAs and blocking the degradation of mRNAs.

d. *mRNA stability and splicing;* lncRNAs regulate splicing and therefore stability.

e. *Regulation of translation;* lncRNAs can inhibit translation utilizing different mechanisms (1,7-9).

Role of LncRNAs in Breast Cancer

LncRNAs with aberrant expression may contribute to tumor development, metastatis and even drug resistance, thereby causing differential prognosis in patients. They are involved in some essential processes such as cell proliferation, migration, DNA damage response, cell-cycle regulation, survival and self-renewal in breast cancer. It has been also determined that lncRNAs exhibit differential expression patterns in distinct subtypes of breast cancer. For this reason, they may have potential as molecular diagnostic and prognostic markers and also therapeutic targets in this type of cancer. Several lncRNAs involved in breast cancer is discussed in below.

HOX antisense intergenic RNA (HOTAIR): It is the first discovered and well-characterized oncogenic lncRNA and located at chromosome 12q13.13. HOTAIR acts epigenetically as a suppressor of HOXD gene and is suggested prototype of of lncRNA-mediated epigenetic modifications. It recruits PRC2 complex to specific genes and leads to histone H3 lysine 27 trimethylation of multiple genes of HOXD locus. Generally HOTAIR expression level is low in normal mammary epithelial cells and increases in primary tumors of breast and also in metastasis. Its high expression in breast tumors is associated with breast cancer lung metastasis (10-11). On the other hand, elevated levels of HOTAIR expression is involved in ER and PR positivity (11). In only ER-positive breast tumors, association between poor prognosis and HOTAIR expression bocomes more powerful. Therefore, this evidence suggests expression of HOTAIR may be used as biomarker for prediction of metastasis risk especially in ER-positive patients with breast cancer. PRC2 is relocalized by HOTAIR to greater than 800 promoters of genes. Chromatin relocalization of PRC2 via HOTAIR causes epigenetic silencing of the genes in the genome related with metastasis suppression (10). It has been published that genes with HOTAIR-induced PRC2 occupancy are repressed in aggressive tumors of breast. Hence, association of HOTAIR with PRC2 has therapeutic value in metastasis of breast cancer (3,10).

HOTAIR was indicated to stimulate migration and invasion in TNBC cell lines. Furthermore, it has been reported upregulation of HOTAIR was highly correlated with metastasis of lymph node in patients with TNBC (12,13). Knock-down of HOTAIR is necessary to improve therapeutic influence of the combination therapy in lapatinib and imatinib (14,15). Future research will hopefully help elucidate role and action mechanism of HOTAIR in development and progression of metastasis in breast cancer.

Since STAT3 pathway has a critical role in breast cancer metastasis, HOTAIR participate this process via inhibition of miR-7 which is negative regulator of STAT3 network and EMT of breast cancer cell (9). MiR-7

inhibits cellular processes through targeting SETDB and decreases the population of breast cancer stem cells and reverses EMT by repressing of STAT3 pathway in cell lines of MCF-7 and MDA-MB-231 and xenograft model (16). Besides, using MCF-7 and MDA-MB-231 cell lines in a study of cancer stem cells, HOTAIR was shown to affect self-renewal, migration and colony formation in stem cells of breast cancer by miR-34a inhibition transcriptionally and SOX2 upregulation. When introduced miR-34a mimics and HOTAIR in cancer stem cells, it has been confirmed that there is an association between HOTAIR and functional regulation miR-34a in breast cancer stem cells. Moreover, arrangement of full length HOTAIR expression was understood to be linked to negative regulation of miR-34a, thus showing that full length of HOTAIR is needed to influence miR-34a regulation, self-renewal, capacity of colony formation in breast cancer stem cells.

Additionally, overexpression of HOTAIR was determined to be linked to p53 induction, thereby modulating proliferation and colony formation in cancer stem cells (17).

LincRNA-regulator of reprogramming (lincRNA-ROR): This lncRNA was shown to be a major regulator of pluripotent stem cells by targeting several transcription factors and human embryonic stem cells that highly expressed. Basically, lincROR controls EMT and metastasis in breast cancer playing oncogenic role. It is around 2.6 kbp and located at chromosome 18q21.31 (18). This lncRNA was determined to induce EMT, increase hypoxia resistance of tumor, invasion, migration and decrease the sensitivity of tumor cells to chemotherapy (19-21). LincROR also regulates p53 pathway negatively through association with heterogeneous nuclear ribonucleoprotein 1 (hnRNP). This leads to inhibiton of p53-mediated arrest of cell cycle and apoptosis (22).

It was also discovered that lincROR performs as a decoy to inhibit the of recruitment of chromatin regulatory factors (G9A) and destroy histone H3K9 modification of Tescalcin promoter which causes metastasis of breast cancer (23). LincROR regulated miR-205 activity by acting as ceRNA and prevented the degradation of miR-205 target genes, resulting in lung metastasis of breast cancer (3). As a ceRNA of miR-145 in the same way, lincROR functions by the loss of miR-141 expression and giving rise protection of pluripotency factors (24). Basically lincROR induces EMT by targeting of ZEB1/2 and TGF-β signalling resulting in modulation of EMT markers for example vimentin and neural cadherin (22, 25-27).

As lincROR is greatly stimulated in breast cancer and its overexpression is connected with poor prognosis in patients, it has been recommended that inhibiting the activity of lincROR may be a strong therapeutic approach (28). In immunodeficient mice, knockdown of lincROR in breast cancer cells was shown to prevent lung metastasis of breast cancer (3).

Metastasis associated lung adenocarcinoma transcript 1(MALAT1): Oncogenic lncRNA MALAT1 is located at chromosome 11q13 and has been first demonstrated to be overexpressed in invasive non-small cell lung carcinoma (NSCLC) (29). It is one of the most conserved lncRNAs among mammals (30). MALAT1 has been suggested to induce strongly PI3K/AKT/mTOR and also Wnt/β catenin pathways in breast cancer as well as some other malignancies (31).

MALAT1 also acts as a sponge for miR-101 and miR-217 which regulate cell cycle and blocks their regulatory function (32). Expression level of MALAT1 was negatively associated with the survival of ER and lymph node negative patients in TNBC and HER-2 subtypes of breast cancer (33). Knockdown experiments using antisense oligonucleotide of MALAT1 indicated impaired cell migration and decreased metastasis (34). Another study has also showed that MALAT1 antisense oligonucleotides repressed development of breast cancer in xenograft luminal B mouse models (35).

Despite these mentioned oncogenic functions of MALAT1, several studies reported that knockout of MALAT1 promoted metastasis and upregulation of MALAT1 blocked metastasis in breast cancer in transgenic and xenograft models (36). The contradictory results of these studies emphasize complex and complicated roles of MALAT1 in metastasis of breast cancer.

NF-kB interacting long noncoding RNA (NKILA): NKILA is a tumor-suppressor lncRNA and located at chromosome 20q13. It suppresses metastasis in breast cancer and reduction of its expression is related to poor prognosis of the patients (37,38).

NKILA was determined to block metastasis of breast cancer by repressing the function of NFkB signalling pathway. This pathway is constitutively induced in breast cancers (9). NKILA performs as a negative feedback regulator of NFkB by its interaction to NFkB/IkBα to form a triplex complex. IKK-promoted phosphorylation of IkBα is blocked since NKILA binding covers the IKK phosphorylating sites. NFkB also mediates TGF-β promoted EMT in breast cancer. During this process, TGF-β increases NKILA expression and thus gives negative feedback mechanism that block induction of NFkB signalling network (38).

Anti-differentiation noncoding RNA (ANCR): ANCR is downregulated in differentiation and is a strong tumor suppressor lncRNA in breast cancer. It has been reported to repress metastasis in immunodeficiency mice. ANCR has been found to cooperate with EZH2 and make easy CDK1 binding to EZH2 to induce its phosphorylation, resulting in EZH2 degradation.

Another action mechanism of ANCR was related to modulation of TGF-β signalling network to block lung metastasis of breast cancer (39,40).

It was suggested that ANCR may join TGF-β1-promoted metastasis via further mechanisms other than EZH2 degradation.

Maternally expressed 3 (MEG3): MEG3 is located at chromosome 14q32.2 and downregulated in breast cancer (41). It has been suggested to act as a tumor suppressor by performing as a sponge for a few miRNAs such as miR-29, miR-21, miR-494, miR-9 (42-44).

In breast cancer, MEG3 was reported to act as a tumor suppressor lncRNA by enhancing p53 expression through inducing the expression of NFkB level (41). Besides, MEG3 was determined to repress PI3K/AKT/mTOR pathway and hence, blocking oncogenic function of highly expressed miR-21 in the cells of breast cancer (45).

Linc-ZNF469-3: Upregulation of this lncRNA is associated with metastatic lesions of lungs in patients with TNBC. There was a negative correlation between overexpression of linc-ZNF469-3 and overall and disease free survival in TNBC. Its upregulation enhances renewal of stem cells and migration and invasion of cell lines in breast cancer by inducing metastasis in lungs of mice. İnhibiting miR-574-5p due to its sponge activity, this lncRNA modulate expression of ZEB-1 to promote EMT, and thus induce lung metastasis. It was clinically shown that upregulated ZNF469-3 and ZEB1 and downregulated miR-574-5p are connected to recurrence of tumor in patients with TNBC (46).

Long intergenic non-protein coding RNA 1683 (LINC01638): It is an important lncRNA involved in the mesenchymal characteristics of TNBC cells. In comparison to normal adjacent breast tissues, Linc01638 is quite upregulated in tumor cells of TNBC. Linc01638 is also upregulated in HER2 positive subtype of breast cancer compared to their matched healthy tissues. Increased expression of linc01638 is associated with worse outcome of patients with TNBC. Cells of TNBC acquire mesenchymal features due to the effect linc01638 by being exposed to EMT and cancer stem cell-like state.

Knockdown studies of linc01638 decreased metastatic lung tumors in recipient mice compared to mice transplanted with control cells, demostrating that linc01638 induces in vivo progression of breast tumors. Linc01638 activates EMT by regulating positively c-myc-mediated metadherin (MTDH) transcription, which is a major controller of metastasis, by stimulation of Twist1 epigenetically. Association of linc01638 with c-myc ultimately blocks c-myc degradation. Restoration of c-myc expression abolished the influence of linc01638 knockdown on the development of metastasis (47).

BMP/OP-Responsive Gene (BORG): LncRNA BORG is a driver lncRNA in chemotherapy resistance of breast cancer and expression levels

are correlates with lnog-term poor prognosis in the patients. Doxorubicin treatment promotes expression of BORG. Once BORG becomes activated, it induces transcriptional response that stimulate survival and drug resistance of TNBC cells. LncRNA BORG regulates one gene which is involved in NFkB activation. BORG stimulates phosphorylation of IkBα and its ultimate degradation. Disposal of IkBα increases phosphorylation and then DNA binding activity of NFkB. Consequently, BORG causes chemoresistance of TNBC by stimulating NFkB signalling pathway (48,49).

In addition discussed lncRNAs above, it has been reported that there are more characterized lncRNAs which are mostly involved in development, progression, metastasis and even chemoresistance of breast cancer (Table 1).

LncRNAs as Biomarkers and Therapeutic Targets

Several lncRNAs have been established as new biomarkers in breast cancer. RNA-seq data from TCGA portal indicated that more than 600 patients with breast cancer are classified to the clinical subtypes based on lncRNAs expression. LncRNA clustering predicted four groups that exhibited different prognosis (50). Moreover, TCGA data analysis of 1097 samples displayed 1510 differentially expressed lncRNAs in healthy control and TNBC samples (51).

Although the most of lncRNAs are still required to be discovered and clinically characterized, this data showed lncRNAs could be utilized as potential biomarkers in diagnosis and prognosis of breast cancer. For instances, overexpression of HOTAIR suggests a unique connection with prognosis of patients with breast cancer due to its involvement in metastasis as mentioned in previous section. Another study reported HOTAIR especially in ER-positive subtypes was associated with poor prognosis. For this reason, HOTAIR might be used as a biomarker for prediction of metastasis in patients with ER-positive breast cancer (11). Since breast cancer is highly heterogenous, exploring new molecular biomarkers like lncRNAs will be extremley valuable to be able to distinguish clinical and molecular subtypes of breast cancer.

An important challange in clinical use of lncRNAs is the lack of quick and reliable tecniques to detect lncRNAs in breast cancer. To analyse lncRNAs easily, researchers are focusing to determine circulating lncRNAs in liquid biopsies via peripheral blood because wide range of lncRNAs are available in the circulation. However, research about circulating lncRNAs is still in early stage and thus, comprehensive studies are needed to apply them in the clinic as diagnostic, prognostic and therapeutic markers.

Most studies verified lncRNAs also have therapeutic potential. It has been shown that silencing of HOTAIR blocked metastasis in breast cancer cells in xenograft mouse models (52). LncRNA NKILA repressed

metastasis in a xenograft model and its low levels were correlated with poor prognosis (37). Depending on their expression pattern, several methods were established to modulate the function of lncRNAs utilizing antisense oligonucleotides (ASOs), RNA interference (RNAi) and gene editing technology such as Clustered regularly interspaced short palindromic repeats (CRISPR)-associated nuclease-9 system (CRISPR/Cas9).

Downregulation of expression of HOTAIR using particular siRNA lead to decreased cell viability and invasiveness in breast tumors (53). On the other hand, engineered ASOs is a strong tool which targets many RNAs regardless of cellular location. For example, progression of breast cancer could be inhibited by MALAT 1 knockdown using ASO (34). LncRNA DANCR is suppressed using specific siRNA and its blocking results in inhibits cell proliferation, invasion and tumor growth in breast tumors. Additionally, inhibition of lncRNA urothelial carcinoma-associated 1 (UCA1) increases tamoxifen sensitivity and reduces tumorigenicity in tamoxifen resistant breast tumors via suppressing Wnt/β catenin pathway (8). SiRNAs could be a good choice for targeting cytoplasmic lncRNAs while ASO might be appropriate for lncRNAs in the nucleus. New technology CRISPR/Cas9 is an effective tool for loss and gain function of lncRNAs. By using CRISPR technology, MALAT1 suppression was accomplished and studied the role of MALAT1 in metastatic incidence of breast cancer (36). Also, it has been shown the knockdown of lncRNA-21A and AK023948 in MCF-7 cells using CRISPR technology (8).

Restoration of tumor suppressive lncRNAs generate blocking effect in breast cancer. Upregulation of of lncRNA CASC2 prevents breast cancer cell growth and metastasis by inhibiting tumorigenic effect of miR-96-5p (8).

To conclude, the discovery of lncRNAs has opened new window in cancer studies. Since they have a great promise to be utilized as molecular biomarkers in diagnosis and prognosis of breast cancer, extensive research is proceeding to develop lncRNA-based next generation markers and therapeutics in diverse types of cancers including breast cancer. Furthermore, gene editing technologies may contribute for exploration novel lncRNA-based therapies. Further investigations are essential to obtain additional information about breast cancer related lncRNAs for development of their therapeutic applications.

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Table 1: Characterized LncRNAs in Breast Cancer and Their Functions

LncRNA	Expression Status	Type	Function	Reference
H19	Up	Oncogene	Sponge let7 family miRNAs	54,55
GAS5	Down	Tumor supressor	Interaction with mTOR signalling pathway, apoptosis	56
PTENP1	Down	Tumor supressor	Upregulates PTEN via its ceRNA interaction on miR-19b	57
EPIC1	Up	Oncogene	Cell cycle progression	58
NEAT1	Up	Oncogene	Metastasis	59
ATB	Up	Oncogene	Promotes EMT	60
UCA1	Up	Oncogene	Wnt/β catenin and mTOR Pathway	61
BCAR4	Up	Oncogene	Hedgehog/GLISignaling Transduction	57
PANDAR	Up	Controversial	Regulation of G1/S transition	7
XIST	Up	Controversial	Brain metastasis and cell growth	62,63
LINKA	Up	Oncogene	Hypoxia Pathway	57
PLNCRNA-1	Down	Tumor supressor	Upregulates TGF-β1 Induces apoptosis Downregulates PHGDH	57
PVT-1	Up	Oncogene	Wnt/β catenin pathway	57
Lnc015192	Up	Oncogene	Migration, invasion, EMT	64
AC026904.1	Up	Oncogene	Metastasis	61
HOTAIR	Up	Oncogene	Epigenetic gene silencing	10-11
MALAT-1	Up	Oncogene	InducesPI3K/AKT/ mTOR and Wnt/β catenin pathways	31
NKILA	Down	Tumor supressor	Metastasis	37-38
MEG3	Down	Tumor supressor	RepressPI3K/AKT/ mTOR pathway Activates p53 Sponge miR-29, miR-21, miR-494, miR-9	41-45
ANCR	Down	Tumor supressor	Invasion and metastasis	39-40
LincRNA-ROR	Up	Oncogene	EMT, invasion, metastasis	19-21
ZNF469-3	Up	Oncogene	Metastasis	46

Chapter 35

MICRORNAS AND GENE REGULATION IN CANCER

Dr. Berna TAN[1]

1 Prof Dr. Berna Tan İstanbul Medeniyet Üniversitesi, Tıp Fakültesi, Temel Tıp Bilimleri
E-mail: brndemircan@hotmail.com

Introduction

MicroRNAs (miRNAs) are short, conserved, non-coding RNA (ncRNA) transcripts about 22 nucleotides in size and they found in both animals and plants (1-3). MiRNAs control gene expression both post transcriptionally and post translationally (4). These molecules are among the most comprehensively investigated and best characterised ncRNAs. A single miRNA can regulate several mRNA, likewise one gene can be targeted by many miRNAs (2,4,5). Although they were initially considered as 'junk' RNA, these small RNAs are now well established key regulators in gene expression and cellular homeostasis (5). According to database of Mirbase (http:www.mirbase.org), it has been demonstrated almost 50 thousand mature miRNA in different species and identified more than 2500 miRNAs in humans. MiRNAs are estimated to regulate gene expression greater of 60% in humans (2,3). They are regarded to suppress target mRNA by binding complementary sequence in the 3' or 5'-UTR and leading to degredation of mRNA or a block of translation (2,5). It has been recently reported that other genomic areas containing exons and promoters can be recognized and bound by miRNAs (6).

Expression patterns of miRs are tissue specific and they are involved in various biological processes, therofore dysregulation in miRNA expression could be associated with pathological conditions including cancer (2,4,5). Aberrant expression of miRNAs is related with tumor formation, progression and metastasis (1). A variety of miRNAs play major roles during the course of tumorigenesis such as cell proliferation, differentiation, apoptosis, invasion, metastasis and survival. Based on their target, miRNAs may have role as either oncogenes (oncomiRs) or tumor suppressors (onco-suppressor miRs) (2). OncomiRs usually increase cell proliferation and metastasis due to their upregulation, in contrast onco-suppressor miRs lead to tumorigenesis due to their downregulation in various type of cancers. The activity of miRNAs have been influenced by epigenetic modifications as well as genetic abnormalities such as mutations, gene amplifications, deletions and chromosomal rearrangements (6). Dysregulation of the steps in mature miRNA biogenesis pathway can also result in changes of miRNA expression in cancer (1).

Since miRNAs play a critical regulatory role in physiological processes as well as pathological processes, they may have tremendous potential to be used as therapeutic targets and diagnostic, prognostic and predicitive biomarkers in cancer. (1-6).

Biogenesis of MicroRNAs

The canonical biogenesis of miRNA consists of nuclear and cytoplasmic steps. RNA polymerase II or III are responsible enzymes for the transcription of miRNAs and a nuclear miRNA gene generates a hairpin

intermediate which is termed ‘primary miRNA’ (pri-miRNA). Many pri-miRNA precursors are capped and polyadenylated. In nucleus, pri-miRNA is first recognized by Microprocessor Complex made up of the RNAase III enzyme, Drosha, and its cofactor DiGeorge syndrome critical region gene 8 (DGCR8). This complex cleaves pri-miRNA and produces precursor miRNA (pre-miRNA) which have 70 nucleotides. Following this, pre-miRNA is transported from nucleus to the cytoplasm through Exportin 5 and Ran guanosine triphosphate (RanGTP) for additional processing.

Pre-miRNA is degraded by RNAase III enzyme Dicer associated to TRBP (TAR RNA binding protein) in the cytosol. Dicer performs the cleavage of terminal loop from the hairpin and forms miRNA duplex which is 22 nucleotide. This miRNA duplex comprises mature miRNA guide strand and a passanger strand that generally degraded. Small duplex is loaded to Argonaute (AGO) protein and is untwisted by Ago N-terminal domain. The miRNA-loaded AGO associates with other cofactors such as GW182 (TNRC6A) and PACT. As a result, miRNA strand is commonly degraded and, guide strand produces RNA-induced silencing complex (RISC) by binding with Ago protein.

RISC is the effector machine in the cytoplasm. It directs single strand mature miRNA to the target mRNA by binding to this miRNA. MiRISC complex interact with the complementary sequences to 3’UTR of mRNA (perfect match) and leads to degradation and translational suppression. However, an imperfect match will result in translational inhibition (1-6).

When full match of the seed region on mRNA target occurs this induces endonuclease activity of AGO-2 and causing mRNA cleavage and destabilization of AGO-2-miRNA association that eventually promote miRNA degradation. In the case of incomplete complementarity, AGO-2 endonuclease enzyme activity is prevented but performes the recruitment of GW182 protein. GW182 becomes associated with polyadenylate-binding protein (PABC) which induces mRNA deadenylation by having poly(A)-deadenylase complexes, PAN2, PAN3 and CCR4NOT. 5’ cap of mRNA transcipts are recognized and removed by decapping enzymes (DCP1, DCP2) which makes mRNA vulnerable to degradation by 5’-3’ exoribonuclease 1 (6).

Regulatory post-transcriptional modifications of miRNA biogenesis factors such as phosphorylation, ubiquitylation, sumoylation is able to alter miRNA processing by linking expression of miRNA with signaling networks. Also, target mRNAs, long non-coding RNAs (lncRNAs) and RNA-binding proteins can control the biogenesis of miRNAs. The biogenesis process of miRNAs is complex and dysregulation of any step would be associated with many diseases, particularly cancer. Thus, multistep biogenesis pathway is regulated both temporally and spatially (3).

RISC assembly plays a major role for miRNAs applying tasks in that four Ago proteins (Ago1-4) are available. Even though human miRNAs are involved in all Ago proteins, Ago 2 is the most highly expressed protein. MiRNA nucleotides 2-8 counted from 5' end of complement miRNA nucleotides form the seed which is crucial for the detection of target mRNA (7).

In contrast to the common consensus that suppression of gene expression by miRNAs only occurs in cytoplasm, some miRNAs, for instance, miR-29b has been shown to be localized predominantly in the nucleus. Besides, other miRNAs can perform their functions by binding to the 5' UTR region or coding sequence rather than 3' UTR region of target mRNA (5).

In translational repression by incomplete binding of miRNA to target mRNA, some mechanisms have been suggested such as avoiding circularization of of mRNAs, inducing ribosome dissociation from mRNAs, slowing elongation, inducing termination and directing co-translational degradation of nascent protein (8).

MiRNA Deregulation in Cancer

Failure of miRNA function occurs as a result of various mechanisms like mutations, deletions, amplifications, epigenetic modifications involving miRNA coding regions, transcriptional regulation by proteins or lncRNAs, and also mutations in the genes responsible for miRNA biogenesis-linked enzymes (Dicer, Argonuate, Drosha, Exportin 5) (9-12). As miRNAs are essential to maintain correct checking of biological processes such as metabolism, cell proliferation and protein synthesis in normal conditions, deregulation of them result in abnormal growth and cell proliferation that support tumor formation, progression and metastasis (1).

Deletion of miR-15 and miR-16 clusters was first established by Calin et al in most samples of chronic lymphocytic leukemia (CLL) patients. This study was the first evidence for the role of specific miRNAs in cancer (13). It was confirmed that miR-15 and miR-16 promote apoptosis by targeting B cell lymphoma 2 (BCL2) in leukemia (14). Numerous studies so far have reported changes of expressions of miRNAs in diverse types of cancers. For instances, let-7 suppress RAS or MYC to prevent tumor formation but it is downregulated in colon, breast and lung cancers (15-17).

In human gastric cancer, upregulated miR-1269 targets RASSF9 gene and induces cell proliferation, cell cycle G1-S transition and inhibits apoptosis via regulation of the AKT and Bax/Bcl-2 signalling pathways (18).Overexpressed miR-487a was demonstrated to be involved in bad prognosis in patients with hepatocellular carcinoma (HCC) by enhancing cell proliferation via AKT network (19). Reduced expression of miRNA-

331-3p inhibited apoptosis and lead to increased cell proliferation in patients with nasopharyngeal carcinoma (20). In oral squamous cell carcinoma (OSCC), miR-9 expression is repressed however restoration of its expression by miR-9 mimics arrest cell proliferation by supressing cyclin-dependent kinase 6 (CDK6) and cyclin D1(21).

The dysregulation of p53 targeting miRNAs miR-192, miR-194 and miR-215 has been suggested to make cancer cells resistant to apoptosis in multiple myeloma (22). Besides, miR-205 and miR-338-3p may block apoptosis through targeting its inhition gene BCL-2 in prostate cancer (23). Fas ligand which is involved in extrinsic apoptotic pathway is targeted and inhibited by upregulation of miR-21-5p in HCC (24). As a transcription factor, p53 also controls the expression of miR-34 family genes (miR-34a, miR-34b and miR-34c). P53 is activated and regulates miR-34 transcription in response to DNA damage and oncogenic stress, which affect cell cycle arrest, apoptosis and senesence (25).

Another transcription factor MYC, repress the expression of genes of miR-26, miR-29, miR-30 and let-7 family members in lymphoma (26-28). The zinc-finger E-box-binding homeobox (ZEB) transcription factors ZEB1 and ZEB2 are shown to be activators to induce epithelial-mesenchymal transition (EMT) and supress miR-200 family gene transcription in breast cancer (29).

By regulating hypoxia-inducible factor 1 α (HIF-1α) and vascular endothelial growth factor (VEGF), tumor angiogenesis can be checked via miRNAs like miR-210 and miR-519c in hypoxia (30). MiR-21 transcription is activated by signal transducer and activator of transcription 3 (STAT3) by binding to miR-21 promoter (31,32). Besides, miR- 21 is known to repress major genes of important tumor suppressive pathways like p53, TGF-β and mitochondrial apoptosis (5). It may be new and promising approaches for the cure of cancer to target or induce specific transcription factors related to some oncomiRs and oncosuppressor miRs.

Expression of miRNAs are also regulated by epigenetic alterations, mainly DNA methylation as well as genetic mutations as mentioned above. Promoter associated CpG island methylation of miR-127 occurs in human bladder cancer and leads to high expression of the target gene, BCL6 (33). Furthermore, epigenetic silencing of miR-124-1 via promoter hypermethylation has been reported in breast, liver, colon, leukemia and lymphoma, and epigenetically suppression of this miRNA cause the activation of its target CDK6 (34,35). In bladder, breast, non small lung cancers, miR-200 has been suggested to be inactivated by epigenetic modification (36). miR-34a, miR34b and c are hypermethylated and silenced in solid tumors and hematological tumors (37,38). Ten eleven translocation family members TETs (TET1, TET2, TET3) are demethylase

enzymes and they restore the expression of methylated miRNAs. TETs can reactivate miR200 epigenetically repressed via promoter hypermethylation. However miR-22 directly targets TETs, thus reactivation of miR-200 is antogonized and metastasis and EMT induced in breast cancer (39). Histone modification which is another epigenetic mechanism as well as promoter DNA hypermethylation controls miRNA expression by chromatin remodelling (40). All of these mentioned miRNAs are associated with tumor development and progression processes including cell cycle, cell proliferation, apoptosis, angiogenesis, EMT and tumor invasion, performing critical roles in the regulation of carcinogenesis.

Cell-free miRNAs exist in various biological fluides such as plasma, serum, urine showing that miRNAs may assist intercellular signalling network and are strong biomarkers for cancer as well as many disease. Some miRNAs are packed into naturally equipped biological vehicles for secretion called exosomes as well as being released by passive leakage from lytic cells. Exosomes are significant vehicles of connection between tumors and close or distant cells. It ranges 30 to 150 nm in diameter and consist of biological components as lipids, proteins, mRNA and miRNAs (1-3). However, adipose tissue is thought to constitute a major basis for circulating exosomal miRNAs (3). These are vesicle-like structures and contain circulating miRNAs, which can circulate whole organism and function in a tissue-dependent manner. After delivering their cargo, exosomal miRNAs can result in reprogramming of the gene expression of the target cells, modulating tumor growth, metastasis, epithelial mesenchymal transition, angiogenesis and immune function. Therefore, exosomes are critical players in the intercellular signalling pathways in the tumor microenvironment. Different studies reported that exosomes are responsible for the stability of miRNAs since their packaging in exosomes avoid them cleavage and provide their stability. Also, miRNAs could be monitored with non invasive approaches because they are transported to vesicular exosomes. It was reported that cell lines of breast cancer secrete high level exosomes in comparison to normal breast cells. MiR-21 and miR-1246 were found to be upregulated in breast cancer patients as compared to healthy controls, thus offering their use as diagnostic and prognostic biomarkers in breast cancer in addition to various kind of cancers (2). Other major part of extracellular miRNAs is exported in cooperation with RNA-binding proteins, such as AGO2, NPM1 (1,3,5). MiR-21, miR-200 family and miR-17-92 cluster are exosomal miRNAs and they are functionally and clinically relevant in tumorigenesis (1).

Numerous research suggest tissue and disease specific miRNAs might have potential as new biomarkers for diagnostic, prognostic and predictive purposes. Crucial role of miRNAs in a wide range of diseases together with the fact that one miRNA may alter the expression status of some genes of

multiple pathways changed in diseases causes miRNAs to become novel therapeutic targets (5).

MicroRNAs as Clinical Biomarkers

As discussed in previous section, dysregulation of specific miRNAs act as key players in the development and progression of cancers since miRNAs may regulate all the charecteristics of malignancy. Therefore, detecting aberrant expression of the miRNAs could be utilized in diagnosis, prognosis, classification and finding predictive biomarkers in cancer. Also, miRNAs could be promising therapeutic targets (8). Thousands published papers are available about the potential use of miRNAs in cancer diagnosis and prognosis. Some of the clinically important miRNAs are presented in Table 1 here.

Tissues as well as liquid biopsies can be utilized as material for determining miRNAs as biomarkers (41,42). As diagnostic and predictive biomarkers, miR-148b-3p, miR652-3p, miR-10b-5p, miR-155, miR-125b, miR-221, miR-365 have been indicated to have aberrant expression in serum samples of patients with breast cancer (43-45). Furthermore, since breast tumors have intrinsic heterogeneity, scientist focus on discovering miRNAs signatures which predict subtypes of breast cancer. Hence, Gasparini et al indicated 4 miRNA signatures (miR-155, miR-493, miR-30e, miR-27a) that identified thee subgroup of triple-negative breast cancer (46).

On the other hand, urinary cell-free miRNAs have been found as potential markers for some urological cancers. One study reported association between urinary miR-126 and hemangiomas in children (47). It has been proposed that miR-25/92a and miR-22/29a levels are high in cervical specimens which suggested diagnostic method of cervical cancers (48). Four miRNAs (miR-498, miR-183, miR-205 and miR-31) are identified as proper signs in urine for benign renal oncocytoma (49). miR-335 has been indicated to inhibit metastatic cell invasion by targeting progenitor cell transcription factor (SOX4) and extracellular matric component tenascin C to repress metastasis and migration of cancer cells (50). miR-411 has been demonstrated to suppress cell growth, migration and invison of breast cancer and its downregulation is associated with lymph node metastasis. These findings show that miR-411 could be used as therapeutic biomarker for breast cancer treatment (51).

Nowadays, computer-aided biomarker discovery becomes common because network systems may function as a biological system for the prediction. Utilizing expressed databases like TCGA and METABRIC, researchers identified novel biomarkers in all types of cancers (3).

MiRNA-Based Therapies

As mentioned before oncomiRs and oncosuppressor miRs have abberrant expression patterns in cancer. While a number of oncomiRs were upregulated in cancer, another set of oncosuppressor miRs was downregulated in tumor development and progression. Correcting the levels of deregulated miRNAs may have a big impact in the treatment of cancer. The development of miRNA-targeted therapeutics has improved markedly in recent years. New pharmacological approaches intent to target various cancers by targeting their regulating miRNAs (4). MiRNA-based therapy in the case of upregulated oncomiRs is established by two strategies. Both of them is based on deactivating specific oncomiRs.

The first one is the miRNA sponges which are also called as competitive endogenous RNAs (ceRNAs). MiRNA sponges are inhibitory transgenes that express many copies of specific miRNA binding site. Thus, they can neutralize target miRNAs by avoiding them interacting with their correspondent mRNAs (2-4). LncRNAs are first discovered miRNA sponges. It was published that lncRNA TUSC-7, is the sponge of miR-146, could disrupt the degradation of the target gene NUMB via inactivation of NOTCH pathway (52). As a sponge of miR-590-3p and miR-1275, the lncRNA FAM225A is upregulated and induces nasopharyngeal carcinoma (NPC) formation by enhancing integrin ß3 which is the target of both miRNAs (53). Tumor progression in NPC is also induced by lncRNA prostate cancer-associated transcript 7 (PCAT7) which acts as a sponge of miR-134-5p (54).

Circular RNAs (circRNA) are naturally occuring miRNA sponges and they are expressed abnormally in tumor samples (3). For instance, CircRNA-7 has been determined to be regulated by miR-671, and in mouse brain it acts as a miRNA sponge of miR-7 (2). In another work, circMMP9 was reported to perform as a sponge of miR-124 and increase the development and migration of glioblastoma multiforme (GBM) cells (55).

The second strategy consists of anti-sense oligonucleotides which are around 18 to 22 nucleotides in size. These synthetic single-stranded RNA molecules have sequence complementary, so interact with a specific miRNA and prevent its binding to 3'UTR of the mRNA (2,5). Anti-miRs can repress miRNA sequnce completely or incompletely. One study reported that miR-21 antisense oligonucleotide can heal trastuzumab resistance in breast cancer (2). Expression of miR-10b is increased in glioblastoma as compared to normal brain tissue. For this reason, anti-miR-10b for blocking the growth of glioblastoma is under phase I study. However, it is not clear whether anti-miR-10b construct leads to off-target effects and specific anti-miR-10b is taken up by glioblastoma (56). Besides, miR-10b antagomir has been utilized in orthotopic xenograft mouse model and

indicated to repress breast cancer metastasis to lungs (57). Anti-miR-21 oligonucleotides decreased the tumor growth by 50% in breast cancer by using the xenograft model (58).

Locked nucleic acid-antisense oligonucleotides (LNA) are used to suppress the expression of endogenous miRNAs. This modification enhances RNA stability of anti sense oligonucleotide and promote the binding capacity for complementary sequence (5). MRG-106 is an anti-miRNA 155 LNA modified antisense oligonucleotide and it targets and blocks oncomir miR-155. MRG-106 is in phase II clinical trials in patients with cutaneous T-cell-lymphoma (CTCL) and mycosis fungoides (MF) who have increased expression of miRNA 155 (59). In phase I study, administration of MRG-106 intratumoral and subcutaneous showed that its inhibitory was well tolerated. Applying MRG-106 directly to the tumor area likely decreased off-target effects (5). LNA inhibitor MRG-110 is used to to decrease expression of miR-92 which is a strong anti-angiogenic miRNA. It is hoped MRG-110 to quicken wound healing by enhancing angiogenesis when applied into the skin at the area of the wound (60).

In the case of downregulated oncosuppressor miRs, miRNA mimics can be used which are synthetic, double stranded oligonucleotides. MiRNA mimics act in similar manner to endogenous miRNAs and improve expression of downregulated miRNAs when introduced in the cells (2,5). MRX34 was the first miRNA mimic to enter phase I clinical trial in patients primary liver cancer metastasis by liver origin. The purpose of this miRNA mimic-based therapy is to cure the task of miR-34 utilizing a synthetic miRNA mimic encapsulated in a liposome. Restoration of miR-34 controlled almost 24 oncogenes associated with cell cycle and proliferation, metastasis, antiapoptosis, chemo-resistance, self-renewal and oncogenic transcription. Even though MRX34 has potent therapeutic implications and safety data in phase I clinical trials, immune-related severe adverse effects occured and hence clinical trial was stopped by biopharmaceutical company (61).

Another miRNA-based therapy is MesomiR-1 which is also in phase I clinical trial and use ‘TargomiR’ technology. This delivery vehicle consists of miR-16 based miRNA mimic and specific EGFR antibody surrounded by non-living bacterial-derived minicells and recognizing protein on the target cell. MesomiR-1 is administered to patients with non-small-cell lung cancer and mesothelioma and aims to replace the function of miR-16 (62). MesomiRs was accepted and related to early anti-tumor activity.

Since miRNA mimics and anti-miRNAs are unstable in vivo due to attacks of nuclease enzymes, these miRNAs-based therapies are not taken up by cells readily and they are not able to bind their targets efficiently. To overcome this challenges some alterations were introduced into cells like

LNA. The miRNA mimics can be administered using viral, lipid vectors and nanoparticles. Despite considearbly efficient for shipping miRNA into the cells, safety of viral vectors limit their use. Lipid vectors are composed of lipid bilayer and help efficient delivery of miRNA that protect from cleavages by nucleases. Cationic liposomes have strong positive results because they have positively charged membrane, which help taking via the negatively charged cellular membrane (2).

In brief, miRNA-based cancer therapies have indicated successfull and promising results in blocking tumor growth, thus miRNA-based therapeutics have nowadays reached to clinical evaluations. However subopitmal in vivo delivery and adverse effects could exhibit difficulty in translating these therapeutic molecules to the clinic. The fact that we understand better the pharmacological properties of miRNA- based compounds as well as safer and more effective delivery technologies will help accomplish innovative non-coding RNA-based therapies.

On the other hand, miRNA-based therapies could be cooperated with conventional chemo and radiation therapy, and so provide new approach for miRNA-based therapy. They might have enormous clinical effects in the pathogesis, diagnosis and treatment of malignancies together with other ncRNAs like lnc-RNAs and circRNAs.

Conclusion

Knowledge in miRNAs is rising more and more, and recent information about their action mechanism on gene regulation has shed new light on cellular networks. Alterations in the expression of specific miRNAs are well established in obtaining of all the published hallmarks of cancer. Clinical uses of miRNAs as molecular biomarkers in cancer diagnosis, prognosis and treatment have still long way to go. Further investigations are needed to explore circulating miRNA biomarkers, and also specific standardized assays are necessary for the quantification of miRNAs in body fluids. Besides, their importance in regulating tumorigenesis is valuable in estimating the prognosis of anticancer therapy and possibly abolishing cancers. Since a number of genes could be targeted by a single miRNA, targeting oncomiRs and oncosuppressor miRs therapeutically is still a challange in the field due to their off-target effects. For this reason, more clinical research is required to improve their stability, off-target effects, and efficacy.

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miRNA	Dysregulation	Cancer Type	mRNA Target	Reference
miR-15, miR-16	Down	Chronic lymphocytic leukemia (CLL)	BCL-2	14
Let-7	Down	Breast, Lung	Ras, Myc	15-17
miR-1269	Up	Gastric	RASSF9	18
miR-9	Down	Oral squamous cell carcinoma (OSCC)	CDK-6	21
miR-192, miR-194, miR-215	Up	Multiple Myeloma	P53	22
miR-127	Down	Bladder	BCL-6	33
miR-26b	Down	Breast	CDK8	63
miR-335	Down	Breast	SOX4	50
miR-200 family	Down	Breast	ZEB1, ZEB2	29
miR-214	Down	Prostate	PTK6	64
miR-944	Up	Advanced cervical cancer	HECW2	65
miR-135a-3p	Down	Ovarian	CCR2	66
miR-122	Up	Breast	PK	67
miR-146b	Down	Breast	NFKB	68
miR-221	Up	Hepatocellular carcinoma	PTEN	69
miR-487a	Up	Hepatocellular carcinoma	AKT	19
miR-205, miR-338-3p	Down	Prostate	BCL2	23
miR-181a-5p	Up	Colorectal cancers	β catenin	70
miR-27a	Up	Breast	ZBTB10	71
miR-191/425	Up	Breast	EGR1	72

Table 1. MicroRNAs in cancer with their target and regulation status

Chapter 36

SELF AND FAMILY PERCEPTIONS OF CHILDREN HAVING CANCER TREATMENT THROUGH FAMILY DRAWINGS*

Sehnaz ILKILIROGLU SAYICI[1]
Banu YAZGAN İNANÇ[2]

1 *This study is based on M.Sc. thesis titled "Kanser Tedavisi Gören 5-10 Yaş Arasi Çocuklarin Kendilerine ve Ailelerine Yönelik Algilarinin Aile Çizimleri Yoluyla İncelenmesi". ilkiliroglusehnaz@gmail.com

2 Prof Dr, Toros University, Department of Psychology, banuyazgan.inanc@toros.edu.tr

Introduction

Childhood cancer is a stressful experience. Cancer is a disease that cannot be explained solely by the recognition of structural and functional changes in cells, tissues, and organs; additionally, it is a social, religious, and cultural illness that is affected by the structure of the family. However, the illness experience poses a particular threat to the family, and chronic diseases such as cancer cannot be seen independently of the family context. (Baider & Goldzweig, 2012). Childhood cancer diagnosis is an event that dramatically changes the lives of children and their families. (Eiser, 2004; Hinds, 1990). When diagnosed with childhood cancer, which is a chronic disease, children and their families suffer from a psychological breakdown despite the opportunity for treatment and survival (Ağaoğlu & Nogay, 2011; Özçelik, 2015). The degree of effect that it has on the child depends on various factors;the developmental stage of the child, the child's reactions and coping capacity , the grade of the disease, family attitudes,nature of the previous parent-child relationship, the type of treatment, possible permanent effects and future limitations, attribution of meaning of the illness, its effects on child's social adaptation, school life, habits, and relationships with siblings and friends (Yörükoğlu, 2013; Er,2006).

Following the diagnosis, the child, family and close social environment of the patient try to understand and evaluate the situation. During the treatment period the child may be absent from the school for a long period. Also, has to endure painful medical intervention and may socially be separated away from the family (Askins & Moore, 2008). Parents are faced with increasing responsibilities. They have to change their routines, roles, responsibilities and relationship patterns and may need to receive supervision for a long period of time (Woodgate 2006). Research results reveal that these difficulties that the child and the family face, are related to physical, psychological and behavioral problems that will occur in childhood, adolescence and even in adulthood (Özçelik, 2015).

Children in treatment often hesitate to express and share their feelings. Also, they seem to avoid asking questions about their treatment process. Nonetheless they prefer to express their feelings and thoughts through drawings. Due to the fact that children like to draw,it is convenient to administer drawing tests. Drawing tests are frequently used as therapeutic communication techniques which give children opportunity to visualize and express their feelings and perceptions of their condition (Yavuzer, 2013; Beytut et al., 2009; Cavusoglu, 2015; Goldner et al., 2015; Matsumori, 2005).

Reducing the negative effects that may arise during these difficult procedures when children receive cancer treatment, requires understanding these children correctly. Verbal communication is often inadequate in understanding what they really feel and how much they are affected during

diagnosis and treatment process. In this sense, children's drawings have great importance. Picture tests used in the clinical evaluation are based on a projective method (Altınköprü, 2003). The word 'projective' is used in a 'reflective'sense. In projective tests, pictures, ink stains and, completed sentences are used as stimuli. Reflection as a concept is based on the 'Reflection Hypothesis' introduced by Freud's (1955) psychoanalytic approach (as cited in Özgüven, 2012). Drawings provide important opportunities in understanding children's thinking and knowledge levels (Kendrick & Mckay, 2004) and have been widely used in assessing emotional and personality disorders since many years. Drawings are useful methods in which important implications are driven in situations where verbal communication is difficult due to both the age and special conditions of children. Pictures that children draw, consciously or unconsciously reflect their view of themselves and their close environment. Since children cannot convey what they feel and think verbally or in writing, drawings are important instruments in this sense. (Veltmen & Browne, 2002). Through drawings, children convey their subconscious desires and inner world . Also drawings, allow children to express their feelings and thoughts, carry significance in evaluating his developmental characteristics. They reveal hidden emotions of their inner world depending on the cognitive and emotional development period of the child, (Samurçay, 2006).

While drawing, children make arrangements by putting many components together such as content, style, form, color, line, and composition to express what they want to express (Malchiodi, 2005). These drawings, drawn from the children's perspective , provide important information to be conveyed in the evaluation of the family structures of the child by reflecting the relationship with the family members and with their parents (Bahçıvan , 2004). Interpreting the drawings provides us with important clues about their internal conflicts and ways they use to deal with them. At the same time, attention should be paid to the general attitude of the individual while drawing, and the overall information given on the picture . The attitudes and behaviors of individuals in drawing the picture are generally related to their perception of life. In this case, it gives us information about the individual's personality and attitudes in different aspects of life (Sechenov, 1996). By looking at the drawings, it is possible to find information about the children's emotions, conflicts in their inner world, their communication with the people around them, and also about their mental state. Due to the abundance of information, it becomes difficult to reach real information. Therefore, experts and researchers such as Leo (1983), Goodenough (1926), Harris (1963), Kellog (1969), Venger (2011), Durkeevich (1990), Muhina (1981), Stepanov (2004), Yavuzer (2016), who analyzed the drawings, stated some common points. These common points are the color choice used by the child, evaluation according to the

lines, the size of the drawings, the placement of the drawing on the paper, and the child's drawing tempo (as cited in Halmatov, 2016).

Analyzing children's drawings provides the opportunity to understand the child from a psychosocial standpoint, as well as helping to select psychological intervention. In this study, children's family drawings were examined from the aspects of reflection of family characteristics and the revelation of emotional and behavioral problems. In the study, psychosocial problems of children in treatment and their family perceptions will be revealed. The aim of the study, was to have a better understanding of the problems and conflicts faced by chronically ill children and their families who provide care and support for their offsprings. There are very few studies investigating chronically ill children's attitudes and feelings towards their families as reflected in their drawings. Therefore this study is believed to contribute to the development of an evaluation list that will enable researchers to evaluate family pictures in future studies.

Research Questions

1.How do children who receive cancer treatment reflect themselves in the family picture test?

2.How do children who receive cancer treatment reflect their parents in the family picture test?

Method

Research Design

This research has been qualitatively designed to reveal family perceptions of children aged 5-10 years receiving cancer treatment, and the phenomenological model was used in the research. Phenomenology involves the individual's description of a conscious experience of a phenomenon. Researcher's aim in this model is to discover each participants world of subjective experiences (Christensen et al.,2011). Phenomenology examines events themselves rather than biased causes. When analyzing children's pictures, what is phenomenologically important is to emphasize openness to various meanings, the context in which they are created, and the worldview of the individual. One way of approaching children's expressions from different angles is for the observer to highlight certain images and discover meanings by looking from various perspectives, and to bring a more holistic view to the children's expressions through drawing pictures. "To look with a phenomenological eye" includes acknowledging and expecting that each child approaches drawing differently and has a unique style of drawing with compositions, shapes, and colors that they like or dislike (Malchiodi, 2005).

There are two reasons behind the use of drawings produced by the participants in the research: First, drawings are a fast way of accessing

the emotional world of the participants. Second, drawings are one of the ways a person can reveal his experiences about a certain subject without any bias (Kearney & Hyle, 2004). The reason that drawings are chosen to reveal family perceptions of the patients in this sample ,and it is believed to provide a way to investigate feelings and thoughts of the patients and allows a concise presentation of the experiences of the chronically ill children in relation with their families. The data was analyzed using content analysis and then was classified into certain categories.

Study Group

The participants of this study consisted of children aged 5-10 years ,who received outpatient and inpatient cancer treatment in two different hospitals affiliated to the Ministry of Health in Mersin and Adana provinces. A total of 26 children participated in the study. The collected data was analyzed using the categorical analysis method. Data was evaluated according to the frequency (f) of indication. Drawings of children undergoing cancer treatment are collected in 4 categories according to their similar characteristics. The categories were specified as drawing level, color selection, missing figures, and exaggerated figure drawing. Results are discussed in light of the theoretical foundations.

Chart 1. *Personal information about the patients who participated in the study*

Personal information of the patients	Frequency (f)
Gender	
Female	10
Male	16
Age	
5-6	11
7-8	6
9-10	9
Type of Treatment	
Outpatient	19
Inpatient	7

Data Collection Tools

In line with the purpose of the study, the patients participating in the study were asked to draw a picture reflecting their thoughts about themselves and their parents. At the end of the drawing, they were asked to explain their feelings and thoughts about their families in clear expressions. The children made their drawings on the blank papers given to them by the

researcher without any intervention after their demographic information was obtained.

Data Collection

The research was conducted with the permission of the Clinical Research Ethics Committee. In line with the permissions obtained, children were given painting paper (paper size 21x29 cm) and 12 colors of dry paint (free of heavy metal-based pigments and substances harmful to health), age-related (for under 8 years old) crayons (free of synthetic preservatives). They were asked to draw 'pictures of their families' on the drawing papers given in the hospital environment. During the data collection, the children were asked questions about their pictures, and the answers were noted.

Data Analysis

The data collected from the drawings were analyzed using the content analysis method. The main purpose of content analysis is to arrive at the concepts and relationships that enable interpretation of the data. In line with this purpose, data are first gathered within the scope (framework) of certain concepts and themes (Yıldırım & Şimşek, 2005).

In the study, the drawings of the sick children were examined in terms of common features, and categories were created by bringing together similar drawings. Pictures that fall under certain categories have been analyzed by relating them to each other. At this stage, the drawings were examined and the unidentified drawings were eliminated. Then, the remaining drawings were examined again and divided into certain categories according to their common features. Finally, the frequency of these categories has been determined.

Generating codes

First of all, the pictures were examined several times at different times, and the sections that were important for the study were determined. While coding, the concepts included in the data were determined by considering the purpose of the research. Themes and categories were created based on the data. The code list that was created has formed a conceptual structure. At the same time, similarities and differences in data features were taken into consideration, and codes with common features were collected under a common theme. Under the most general themes, categories were created and codes were placed under them.

Creating categories

A category is the collection of the obtained codes under certain themes. It is about examining the concepts, determining the related ones, and explaining them with a higher theme (Yıldırım& Şimşek, 2008).

During the analysis phase, the researcher examined both the pictures and the notes taken during the drawings many times and created a list determining the categories. Appropriate categories were created considering questions related to the purpose of the study. Categories that were created: Drawing level, color selection, missing figure drawing, and exaggerated figure drawing.

Validity and Reliability

To ensure the validity and reliability of the research, strategies such as examining and reviewing whether the data is consistent within itself, using direct quotations, participant verification, researcher stance, intense and rich description, asking participants about the picture after the drawings, and asking the colors they like, creating coding accordingly and the suitability of the coding were used.

The first method used to ensure internal reliability in this study was participant verification. Participant verification requires reaching some of the people from whom the data was obtained or interviewed and receiving feedback on the findings obtained (Merriam, 2013). The patients who participated in the study were asked questions about the drawings, and the themes and codes that emerged at the end of the analysis process were checked.

Another internal validity strategy is an expert review. The expert review involves examining raw data by an expert and checking whether the findings obtained based on them are reasonable (Merriam, 2013). Therefore, the themes and categories created as a result of the analysis were evaluated by an expert in qualitative research. As a result, the suggestions of the expert were taken into consideration and necessary corrections were made.

External reliability is about coding the same text by the same researcher at other times and evaluating to what extent the data obtained in a study can be applied to different situations. One of the methods applied for this is a rich and intense description. The participants and the environment, participant interviews, research notes, and quotations from the data should be well described in detail (Merriam, 2013). In this study, the data collection process and the descriptions of volunteer teachers were used in the method and discussion part. In the findings section, quotations were frequently used.

Another strategy used is ensuring consensus among coders (Bilgin, 2006). The drawings obtained in the study were examined by another expert trained in this field, and themes and categories were created according to their views. As a result of the analyses, the themes and codes created by the two researchers were compared. During the coding of the researchers, a list of themes and codes was created and an 85% similarity was found between the two lists. Themes and codes of disagreement were discussed, the consensus was achieved on the differences and they were rearranged.

Findings

In this section, children's drawings of self and parents are classified into some conceptual categories and subcategories and converted into numerical valves. The findings were analyzed in four categories after the evaluation: "drawing level," "color selection," "missing figures," and "exaggerated figures."

In Table 1, the drawing levels of the children receiving treatment are shown according to how they reflect themselves and their parents.

Table 1.

Drawing Level	Child	Mother	Father
Drawing Power		Frequency	
Dark	21	19	19
Faint	5	7	7
Total	26	26	26
Area of the Line			
Right	17	11	10
Left	9	15	16
Bottom	17	12	12
Top	9	14	14
Small	18	10	20
Large	8	16	6
Total	78	78	78
Drawing sequence			
Last	16	9	8
First	10	17	18
Total	26	26	26

When Table 1 is examined, it is seen that the drawings that were made by children in treatment to explain the concept of how they draw themselves and their parents are divided into 3 sub-categories in the drawing level category.

When the drawings constituting the drawing power sub-category in Table 1 are examined, it is seen that the children mostly draw themselves dark (f = 21) and there are only a few faint drawings (f = 5). It has been observed that most of the children draw themselves in their drawings by pressing the paint hard. When the drawings in the drawing area sub-category are examined, it is seen that in most of the drawings, children

drew themselves on the right side (f = 17) and at the bottom (f = 17) of the paper, while the remaining children drew themselves on the left side (f = 9) and at the top (f = 9) of the paper; while those who draw themselves small (f = 18) are in majority, few draw themselves large (f = 8). When the drawing sequence sub-category is examined, it is seen that they mostly draw themselves the last (f = 16), and some the first (f = 10). When the drawings are examined, it is seen that the majority of them drew themselves last, while the remaining drew themselves first.

When the drawings constituting the drawing power sub-category in Table 1 are examined, it is seen that most children drew their mother dark (f = 19), while a small number drew them faint (f = 7). When the drawings in the drawing area sub-category are examined, it is seen that in most of the drawings, the children drew their mother on the left side (f = 15) and at the top (f = 14) of the paper, while the remaining drew them on the right side (f = 11) and at the bottom (f = 12) of the paper; those who drew their mother large (f = 16) are more than those who drew them small (f = 10). When the drawing sequence sub-category is examined, it is seen that the children drew their mother first (f = 17) and last (f = 9). When the drawings are examined, it is seen that the majority of them drew their mother first, while the remaining drew them last.

When the drawings that constitute the drawing power sub-category in Table 1 are examined, it is seen that most children drew their father dark (f = 19), while a small number drew them faint (f = 7), and most of the children drew them by pressing the paint hard. In the drawing area sub-category, it was observed that most of the children drew their father on the left side (f = 16) and at the top (f = 14) of the paper, while the rest drew them on the right side (f = 10) and at the bottom (f = 12) of the paper, the number of the ones who drew their father small (f = 20) is bigger than the ones who drew them large (f = 6). When the drawing sequence sub-category is examined, it is seen that they drew their father first (f = 18) and last (f = 8). When the drawings are examined, it is seen that most of them drew their father first.

In Table 2, color choices regarding how children receiving treatment reflect themselves and their parents are given.

Table 2.

Categories: Color Choices			
	Child	Mother	Father
Codes		Frequency	
Color Choice			
Black	7	7	12
Blue	7	4	3
Red	4	4	1
Yellow	4	5	4
Pink	2	1	0
Orange	1	1	3
Green	1	3	0
Brown	0	5	3

In Table 2, when the drawings drawn by the children receiving treatment to explain the concept regarding how they draw themselves and their parents are examined, 7 distinct colors are collected under the 'color choice' category.

Table 2. When examined, while the colors most preferred by children when drawing themselves are black (f = 7) and blue (f = 7), the colors preferred afterwards are red (f = 4), yellow (f = 4), and pink (f = 2); the least preferred colors are orange (f = 1) and green (f = 1).

When the drawings that make up the color choice subcategory in Table 2 are examined, it is observed that they mostly used black (f = 7) when painting; then preferred brown (f = 5), blue (f = 4), and green (f = 3), and least preferred orange (f = 1) and pink (f = 1).

As it is seen in Table 2, when depicting their father in their drawings, children mostly use black (f = 12), followed by yellow (f = 4), blue (f = 3), brown (f = 3), orange (f=3) and red (f = 1).

Table 3 shows the missing figures used by the children receiving treatment to reflect themselves and their parents.

Table 3.

Categories: Missing Figure Drawing			
Codes			
	Child	Mother	Father
Face		Frequency	
Ear	24	19	24
Nose	16	15	18
Mouth	6	3	5
Hair	6	2	2
Eye	3	2	1
Total	55	40	50
Body			
	Child	Mother	Father
Hand	16	16	17
Foot	11	13	13
Arms	5	2	4
Legs	2	0	0
Total	34	31	34

When Table 3 is examined, it is seen that two subcategories, namely face, and body, have emerged in the missing figure category in the drawings of the children receiving treatment about how they draw themselves and their parents.

When the drawings that make up the face subcategory in Table 3 are examined, it is seen that mostly the ears are missing (f = 24), then the nose (f = 16), hair (f = 6), and mouth (f = 6), and the least missing figure is the eyes (f = 3). Looking at the 'body' sub-category, it is seen that the highest number of them did not paint the hands (f = 16), then feet (f = 11), arms (f = 5), and the legs (f = 2).

When Table 3 is examined, it is seen that the children drew the hair (f = 10), mouth (f = 9), eyes (f = 9), and head (f = 9) of their mother in exaggeration, while the least exaggerated figure is the ears (f = 1). In the 'body' sub-category, it is seen that the feet (f = 8), hands (f = 5), and arms (f = 4) were drawn the most exaggerated, while the shoulders (f = 2) were the least exaggerated.

When the drawings belonging to the 'face' sub-category are examined, it is seen that the children drew the ears (f = 24), nose (f = 18), mouth (f = 5), of their father in exaggeration, while the least exaggerated figure are the hair (f = 1) and eyes (f= 2) . In the 'body' sub-category, feet (f = 8),

arms (f = 7), and hands (f = 6) were drawn, while the least exaggerated one is the shoulders (f = 2).

Table 4 shows the exaggerated figures the children receiving treatment used to reflect themselves and their parents.

Table 4.

Categories: Exaggerated Figure Drawing			
Face			
	Child	Mother	Father
Codes		Frequency	
Hair	13	10	6
Mouth	9	9	10
Eye	6	9	8
Nose	4	0	2
Head	3	9	4
Ear	1	1	1
Total	36	38	31
Body			
	Child	Mother	Father
Arms	8	4	7
Foot	6	8	8
Hand	4	5	6
Legs	0	0	0
Shoulders	1	2	2
Total	19	19	23

When Table 4 is examined, it is seen that two subcategories, namely face, and body, have emerged in the exaggerated figure category in the drawings of the children receiving treatment about how they draw themselves and their parents.

Looking at Table 4, it is seen that in the 'face' subcategory, the most exaggerated figure when children drew themselves is hair (f = 13), followed by mouth (f = 9), eyes (f = 6), nose (f = 4), head (f = 3) and the least exaggerated figure is the ears (f = 1). When the 'body' sub-category is examined, it is seen that the arms (f = 8) are the most exaggerated; then the feet (f = 6), hands (f = 4), and the least exaggerated is the shoulders (f = 1).

Looking at the 'face' subcategory in Table 4, it is seen that the children drew hair (f = 10), mouth (f = 9), eyes (f = 9), and head (f = 9) of their mother in exaggeration, while they drew the ears (f = 1) of their mother

least an exaggeration. In the 'body' sub-category, it is seen that the feet (f = 8), hands (f = 5), and arms (f = 4) were drawn the most exaggerated, while the shoulders (f = 2) were the least exaggerated.

When the drawings belonging to the 'face' sub-category are examined, it is seen that the children drew the mouth (f = 10), eyes (f = 8), hair (f = 6), and head (f = 4) of their father in exaggeration, while the least exaggerated figure are the nose (f = 2) and ears(f=1). In the 'body' sub-category, feet (f = 8), arms (f = 7), and hands (f = 6) were drawn, while the least exaggerated one is the shoulders (f = 2).

In this part of the findings, the evaluations made according to the samples selected from the children's family pictures take place.

Figure 1. *Family picture example, age 7*

Figure 2. *Family picture example, age 6*

In Figure 1 and Figure 2, examples representing the category of drawing level regarding children's family pictures are presented.

Figure 3. *Family picture example, age 6*

Figure 4. *Family picture example, age 6*

In Figure 3 and Figure 4, examples representing the color choice category of children's family pictures are presented.

Figure 5. *Family picture example, age 5*

Figure 6. *Family picture example, age 6*

In Figure 5 and Figure 6, examples representing the missing figures category of children's family pictures are presented.

Figure 7. *Family picture example, age 5*

Figure 8. *Family picture example, age 8*

In Figure 7 and Figure 8, examples representing the exaggerated figures category of children's family pictures are presented.

Discussion and Conclusion

Drawing is considered as a universal language of childhood (Rubin, 1984) and it is one of the best tools for children to express their feelings, thoughts, and experiences. Today, there are still discussions on the reliability and validity of children's drawings. With this in mind, for the purpose of increasing reliability of drawings and reducing limitations of the data, children were asked to explain their drawings verbally, then the drawings were evaluated together with the information stated in the family information form. Additionally, expert opinions were also collected for the categories and the coding system planned to be used in the evaluation process. In the study,5-10 years old children were asked to draw themselves and their families. Based on the common features of the drawings examined, they were categorized into four groups mainly being "drawing level," "color choice," "missing figures," and "exaggerated figures."

The results reveal that, for "drawing level," most children drew themselves small and last, by pressing the crayon hard and placing themselves on the lower right corner of the page. These findings are in concordance the findings of the studies of Venger (2011) and Abdi et al. (2004). In Venger's (2011) study, the lines were drawn by pressing the crayon hard which was stated as an indication of emotional tension and high anxiety level. Similarly, in the study of Abdi et al. (2004), it was found that children with high anxiety levels press the crayon in their drawings. In this study, "drawing level," evaluation revealed that children drew themselves pressing the crayon hard and placing themselves on the upper left corner of the page; they drew their mother large and their father small like themselves. According to Koppitz (1968) children unwillingly reflect their negative feelings towards their families in family drawings by not drawing the shape of their family members properly. Exclusion of family members, the size and position of the figure, and the order in which the family members are drawn are very important in the analysis of children's drawings. While the person who is drawn first to the far left of the page is the person they like and value the most, that person may also be the person with whom they have the most conflicting and difficult interaction, and have difficulties in getting closer with that family member (Bahçıvan, 2004). There may be dependency issues with this family member, usually being the parent. It is stated that the person (usually the child) they draw on the right side of the page as looking to the right side, needs to get away from the family and strive for independence. (Bahçıvan, 2004).

As for "color choice," category, children mostly used black and blue colors for self and black, brown and yellow for mother figures. Also black was used mostly for the father figures. Findings reveal similarity with the studies of Perkins (1977); Greorian, DeMaria & McDonald (1996); and Beytut, Bolışık, Solak & Seyfioğlu (2009). In a study conducted by Greorian, DeMaria, and McDonald (1996) on children who were traumatized in an earthquake, it was found that children drew the sun in black. The black sun figure symbolizes concepts like hopelessness, fear, darkness, and death (Malchiodi, 2005). In Perkins study the sample included both healthy and sick children, and it was found that children with serious fatal illnesses use various colors in their paintings that indicate awareness of their condition. The most commonly used color by ill children is black (Malchioldi, 2005). As similar to this study's findings, blue color indicates control, the black color indicates the intensity of reactions such as fear and excitement (Linderman, 1997). According to Venger (2011), the use of black, gray, and dark brown colors often indicate depression. While there is a choice of all colors, if the child uses a few colors only, it is interpreted as a sign of fatigue, passivity, and even depression. It is thought that children reflect themselves with emotions such as fear, distress, and anxiety brought on by the illness.

The evaluation of "missing figures" category were realized in two groups as "face" and "body." In the drawings, missing figures were ears and nose respectively in the 'face' sub-category; whereas in the 'body' sub-category, the majority of children did not draw their hands and feet. While drawing the mothers and fathers, the ear and nose were mostly missing in the face sub-category and the hands and feet were mostly missing in the body sub-category, showing similarity with self drawings. As started by Machover (1949), when children's drawings are interpretated through psycho analytical perspective; those children who feel inadequate tend to draw smaller human figures (Burns & Kaufman, 1972).

If children have erased or did not draw a part of the body at all ; it should be thought that there is a conflict regarding that region (Altınköprü 2003). Koppitz (1968) identified thirty factors defined as "emotional indicators," which are rarely seen in the drawings of healthy children. These factors are more common in the drawings of children with mental and emotional disorders. Emotional indicators are divided into three categories , first being absence, transparency, and excessive symmetry in body parts; second, unusual elements (such as rain, birds, teeth, and clouds);and third, lack of hands, legs, and eyes . If a child exhibits more than one emotional indications in the picture, it is evaluated as having experiences of anxiety, depression or emotional problems (Koppitz, E., 1968). Marvin Klepsch and Laura Logie (1982), in their work titled 'Children Draw and Tell,' provide the following psychological explanations about the missing parts in children's pictures. While not drawing the hands symbolizes that the child is having difficulty in adapting to the environment and disorder; feet symbolize that the child feels unsafe and helpless. The ear figure in the children's drawings can give information about their social relations. If the ears are not drawn even though they should be visible, it can be concluded that the person has problems in their social relations and experiences inadequacy in their relations (Altınköprü, 2003; Bahçıvan , 2004). The nose is the symbol of the power struggle. The absence of a nose indicates the child's weakness (Yavuzer, 2014). The child symbolizes the members he has conflicts within the family in different ways. Sometimes they draw some elements, arms, and legs either incompletely or distorted (Altınköprü, 2003). Similar to this research findings, Fihrer and McMahon (2009) stated that the family drawings of the children whose mother has depression have higher "general pathology" characteristics. While drawing the family together is seen as a positive characteristic in the family drawings , the presence of missing figures in the family members and themselves is seen as a negative characteristic.

Drawings that constitute the category of "exaggerated figures" are examined in two groups as "face" and "body." it was observed that children mostly drew their hair and mouth in exaggeration in the 'face' sub-category and they mostly drew their arms and feet in exaggeration in

the ‘body’ sub-category. Marvin Klepsch and Laura Logie (1982) made a psychological evaluation of this situation from 3 aspects in their work titled ‘Children Draw and Tell.’ The first one is exaggerated lines in the child’s drawing. It is often used for aggressive children with poor internal control. When the findings of the ‘face’ sub-category are examined, it was seen that the hair, mouth, eyes, and head of the mothers were drawn in exaggeration; while the feet and arms of the mothers were drawn in exaggeration in the ‘body’ sub-category. In the ‘face’ sub-category, the mouth and eyes of the fathers were drawn in exaggeration; while the results of the ‘body’ sub-category were similar as mothers. The hair drawing by pressing the crayon hard shows the child’s desire to be stronger physically. Drawing the hair of the parents by pressing the crayon hard can give a clue about the desire to establish authority and to have a say in the family (Bahçıvan, 2004). If the mouth is a well defined, open mouth, it shows the desire to talk to people; whereas the closed, narrow, line-shaped mouth indicates the hesitation to communicate with people. It is also seen in children who express their anger with swearing and curses. It is thought that it can also be a symptom of orality (Altınköprü, 2003). Exaggerating the mouth shows whether the child tends towards verbal aggression and has a communication problem with the immediate environment, especially with the parents (Şahin, 2017). The arms open to two sides are seen in the drawings of loving people who establish close relationships with people. Sometimes it is an indication of the desire to establish close relationships with people. Arms drawn adjacent to the torso are seen in the drawings of people who have difficulty in establishing relationships with people. The length of the arms is also important. The arms which are drawn longer than usual ,express power and control, while the arms drawn shorter, express lack of apparent desires. The way arms, hands, and fingers are drawn can help explain behaviors such as fear, shyness or hostility, and aggression (Di Leo, 1983; Altınköprü, 2003). While the body and shoulders with rounded and soft lines show humanitarian features, angular and hard body lines may indicate the presence of aggressive impulses. It is seen that people drawn with hard body lines solve their problems by using physical violence (Bahçıvan, 2004). Exaggerated feet are the symbol of the child’s desire for self-confidence. Sometimes it is an indication of the desire to establish close relationships with people. Arms drawn adjacent to the body are seen in the drawings of people who have difficulty in establishing relationships with people (Di Leo, 1983; Altınköprü, 2003). The dominant mother or father, regardless of their physical size, is generally drawn larger than other family members. However, in some cases, children drew the mother figure meticulously, which may be due to their admiration for the mother (Yavuzer, 2014). Feet, especially feet drawn with exaggeration, are the symbol of the child’s desire to have self-confidence (Yavuzer, 2009). Drawing the arms in exaggeration may reflect the symbol of power and force (Şahin, 2017). If the hands are drawn larger than usual, this may mean

compensation for a lack and weakness that the person feels. (Altınköprü, 2003). Exaggerated drawings of hands can also reflect the symbol of desire for power and force (Şahin, 2017). In their drawings, children express the family member with whom they have conflicts with, in different ways. They often draw these members in exaggeration whom they perceive as strong, whom they think to represent authority, and with whom they communicate more often. The dominant mother or father is depicted with an exaggerated physical size compared to others (Yavuzer, 2014).

In present study, children draw their father with the same characteristics as themselves, except for drawing themselves last and on the right side of the paper; whereas they draw their mother significantly bigger. This shows that children need the approval of their individuality by their mother (Bahçıvan, 2004). It has been observed that children used black crayon excessively, generally pressed the crayon while drawing , drew the same parts of both themselves and their parents incompletely, and they drew the same parts of themselves and their mother in exaggeration. These findings indicate that children are pessimistic and depressed, they need a sense of security, their anxiety levels are high, and they see their mother, with whom they communicate more often , as a stronger individual. These findings are in accordance with studies conducted by Marvin Klepsch and Laura Logie (1982), Koppitz (1968), Malchioldi (2005), Venger (2011), Yavuzer (2014), and Halmatov (2016).

The family is of primary importance in shaping any child's behavior. The origins of conflicts and problems that are faced by the child and his inner world ,should be sought in the interaction patterns of the family (Bahçıvan, 2004). The family, who is faced with unexpected, stressful and traumatic conditions has to adapt to these conditions so is the child himself. Medical stuff, educational institutions, and close social environment are expected to help the child and the family to adjust to this new and unexpected conditions of traumatic nature. (Karakavak & Çırak, 2006). This research, is aimed to investigate the role of relevant cues of self and family perceptions of chronically ill children, through their drawings. This technique can be used widespreadly to communicate with children especially with those having cancer treatment., provided that the stuff has adequate training. Psychologists who are working in medical institutions can be great help for families and children of this sort.

In this study, variables such as socioeconomic characteristics of the family, divorce, domestic violence, as such was not investigated. In future studies, these children's relations with their healthy siblings can be investigated as well. Also using triangulation method qualitative interviews can be used along with children's drawings. Comparison of healthy and chronically ill children's drawings can be also compared in terms of family perceptions and family drawings.

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Chapter 37

CEREBRAL INVOLVEMENT IN COVID-19

Asst Prof Osman Ersegun BATCIK[1]

1 Rize Recep Tayyip Erdogan University Medical Faculty, Department of Neurosurgery, Rize, Turkey, e-mail: osmanersegun@gmail.com

When the first cases of the novel coronavirus have emerged in Wuhan province of Hubai state in China at the end of December 2019, the disease seemed to involve only the respiratory system Respiratuar symptoms have become more severe as the disease progressed. A number of studies, mainly from China, have reported the main symptoms as fever, shortness of breath and dry cough. However, after the disease caused by this virus has spread swiftly all around the world, and the number of new cases and death have become to increase incrementally, new studies have been reported from many countries worldwide and new symptoms have been addressed. Today, to our knowledge, COVID-19 affects several other organ systems in addition to the pulmonary system with neurological/cerebral system are the most affected. There are still too much thing to understand about manifestations of the virus and too long way to go in fighting against the virus and eradicate it. It is critical to know the mechanisms of cerebral involvement and neurological manifestations of the COVID-19 infection in order to recognize all possible symptoms caused by the novel coronavirus to diagnose and treat patients timely. As it is discussed in this chapter, reports in the literature on neurological aspects of the disease are scarce. It seems that the COVID-19 will – unfortunately – continue to spread and affect millions people, at least for near future. This will of course lead to the publication of new studies on various manifestations of the disease, adding to our existing knowledge. Cerebral involvement in COVID-19 is addressed in two sections as the possible mechanisms of the involvement and related neurological manifestations.

Cerebral involvement in COVID-19

New features of the new emerging coronavirus, known as Severe Acute Respiratory Syndrome (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) are increasingly being reported as the pandemic caused by the virus spreads all over the world. Unfortunately, the spread can not be stopped, even decelerated, and new manifestations of the virus in the human body are being seen every passing day. In the beginning of the outbreak, COVID-19 virus has been thought to preferentially affect the respiratory system, but later on several other organs and organ systems have been reported to be involved. Among the systems that are reportedly influenced by virus, cardiovascular system, gastrointestinal system and central nervous system (CNS) are the most remarkable ones. SARS-CoV-2 virus may invade CNS and may be responsible for neurological signs and symptoms because of its similarity with other coronaviruses in terms of infection pathways (Zhu et al. 2020).

The exact mechanism through which SARS-CoV-2 virus affects the nervous system has not yet been fully understood. Nevertheless, some studies in the literature have proposed some mechanisms in the body

through which COVID-19 can affect the CNS (Li YC et al. 2020). There are numerous reports on cerebral involvement in COVID-19 (Koralnik et al. 2020, Ghannam et al. 2020). Cerebral involvement has been reported in up to 40% of patients with confirmed COVID-19. Furthermore, SARS-CoV-2 virus has been isolated from cerebrovascular fluids of patients diagnosed with COVID-19 (Moriguchi et al. 2020). Studies in the literature have reported that cerebral involvement was more commonly in severely ill COVID-19 patients than non-severe cases. In a study by Mao et al. from China, a total of 214 COVID-19 patients were divided into two groups according to the severity of the disease. Cerebral involvement and nervous system symptoms were significantly more common in the severe COVID-19 group (45.5% vs 30.2% (Mao L et al. 2020).

Mechanism of Cerebral Involvement

Although there is not enough experimental evidence on how COVID-19 virus invades the central nervous system (CNS), as the virus is thought to be a mutation of previously seen Severe Acute Respiratory Syndrome (SARS) CoV and Middle East Respiratory Syndrome (MERS) CoV, the novel coronavirus is expected to act in a similar way with these two coronaviruses, and also to invade the brain through the same or similar or mechanisms (Wu et al. 2020). Primary target of coronaviruses is respiratory epithelium. The spikes of coronaviruses attach to and enter cells through the angiotensin converting enzyme-2 receptor (ACE 2), and then coronavirus RNA is released into cytoplasm, translated and replicated. An envelope protein forms and RNA incorporated into the coronavirus is spread through the circulation (Baig et al. 2020). Coronaviruses have an opportunist neurotropism. They escape from immune response and interact with ACE 2 receptors to enter the neural issues (Baig et al. 2020). Since ACE2 receptors are also found in the glial cells in the brain, spikes of the COVID-19 virus can attach to these receptors and damage the neuronal tissues. Viral replication resulting in increased activation of ACE-2 receptors in the central nervous system may trigger an inflammatory response leading to an increase in the permeability of the blood-brain barrier and immune-mediated inflammation (Wu et al. 2020). It has been shown in an animal study that, the coronavirus enters the brain through the olfactory bulb, in which the sensory neurons connect nasal cavity with the central nervous system, pass through the cribriform plate, and reaches the brain in seven days (Li Y et al 2020, Manji et al. 2020). Furthermore, the virus can directly reach the brain by disrupting the blood brain barrier (BBB) during the viremia phase. Another possible mechanism proposed for the entry of COVID-19 to the CNS is through the synapse connected pathway. The potential routes of cerebral involvement by COVID-19 are shown in Figure 1.

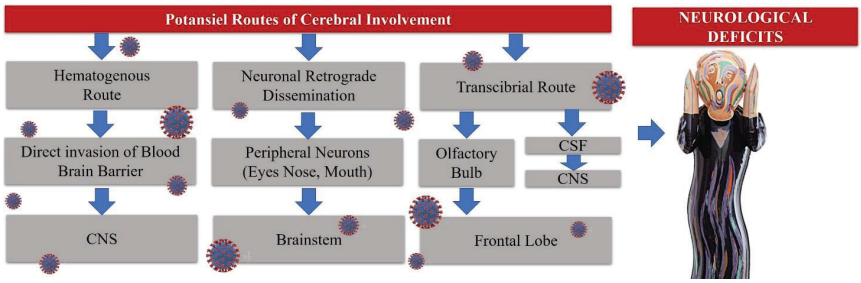
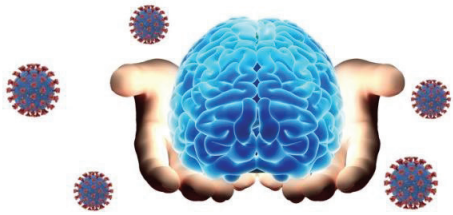


Figure 1. *The potential routes of cerebral involvement by COVID-19.*

Neurological manifestations of the COVID-19

Neurologic manifestations mostly develop in the early stage of COVID-19 as well as may be the presentation symptoms due to this disease (Lechien et al. 2020, Zhao H et al. 2020). These symptoms cannot be treated with antibiotics and require antiviral treatment, as respiratory manifestation of the virus. It is of paramount importance to recognize and manage neurological and cerebral manifestations of COVID-19 timely as they can progress and require urgent intervention. Studies in the literature have reported several neurological manifestations and complications due to COVID-19 including headache, dizziness, delirium, encephalopathy, hypogeusia, neuralgia, acute cerebrovascular disease and impaired consciousness (Liu et al. 2020; Mao L et al. 2020; Helms et al. 2020). For a more detailed analysis, neurological manifestations caused by COVID-19 can be examined under two titles according to the affected system as the central nervous system (CNS) and peripheral nervous system (PNS). These complications and manifestations will be discussed below. The most commonly encountered neurological complications and manifestations of the COVID-19 are shown in Figure 2.



CENTRAL NERVOUS SYSTEM
- ✓ Dizziness
- ✓ Headache
- ✓ Acute Cerebrovascular disease
- ✓ Impaired consciousness
- ✓ Transverse myelitis
- ✓ Ataxia
- ✓ Epilepsy
- ✓ Encephalitis
- ✓ Encephalopathy

PERIPHERAL NERVOUS SYSTEM
- ✓ Hypogeusia
- ✓ Hyposmia
- ✓ Guillian Barre syndrome
- ✓ Neuralgia
- ✓ Skeletal muscle injury

Figure 2. *Neurological complications and manifestations of the COVID-19*

Central Nervous System Manifestations of COVID-19

Dizziness: Historically, dizziness has been associated with viral infections (Saniasiaya and Kulasegaran 2020). In recent times, vertigo or dizziness have been reported as a clinical symptom of the COVID-19. The proposed mechanism by which COVID-19 causes dizziness include direct invasion of the virus, hypercoagulopathy, hypoxia, and immune-mediated response (Wu Y et al. 2020, Shaikh et al. 2020). Studies in the literature from many countries all over the world are increasingly reporting dizziness as a major manifestation of COVID-19. Dizziness has been suggested to occur in COVID-19 following neuroinvasion of SARS-CoV-2 virus. In a study from China, dizziness was stated to be the most common neurologic complication of COVID-19 (Mao L).

Headache: Respiratory viruses are known to cause neurologic symptoms with headache being the leading (Bohmwald et al. 2018). Nowadays, cerebral and neurological involvement by COVID-19 is increasingly reporting, and the most common finding among the neurological symptoms seems to be headache. The rate of headache among COVID-19 has been reported as 11-14% both in the studies investigating both died and recovered patients (Borges et al. 2020, Zhang X et al. 2020, Chen T et al. 2020). On the other hand, there are studies reporting much higher rates of headache. In a study with healthcare workers who had mild symptoms of COVID-19, the rate of headache was reported as 71.1% in those with COVID-19 positivity (Tostmann et al. 2020). However, a detailed mechanism of headache in this disease has not been discussed by any study.

Acute cerebrovascular disease: Inflammation is recognized as a major contributor to the pathophysiology of cerebrovascular disease (Iadecola and Anrather, 2011). Acute cerebrovascular disease associated with the COVID-19 infection has infrequently been reported in the literature. In a study from China, 11/229 patients developed new-onset cerebrovascular disease following COVID-19 infection. In these patients, the median duration between the development of cerebrovascular disease and being diagnosed with COVID-19 was 10 days. All the patients who developed cerebrovascular disease had increased inflammatory response and hypercoagulable state (Li Y, Li M et al. 2020). Patients with cerebrovascular disease were more likely to have cerebrovascular risk factors. Older patients and those with comorbidities such as hypertension, high coagulation state and diabetes mellitus are at a higher risk of developing acute cerebrovascular disease induced by the COVID-1.

Impaired consciousness: The incidence of consciousness disturbance related to the COVID-19 infection has been associated with underlying comorbidity (Guan et al. 2020). In a meta-analysis of studies conducted about the neurological manifestations of COVID-19, the pooled incidence of COVID-19 induced consciousness disturbance was reported as 3.8% (Pinzon et al. 2020). Although impaired consciousness has been reported together with the other neurological manifestations by several reports in the literature (Ng Kee Kwong et al. 2020, Niazkar et al. 2020, Rahman et al. 2020), there is no study specifically addressing consciousness disturbance due to the COVID-19 infection.

Transverse myelitis: The etiology of transverse myelitis includes para- postinfectious, drug or toxin induced, autoimmune disorders (Beh et al. 2013). Acute transverse myelitis is a rare, but serious complication of COVID-19. Similar to many neurological complications caused by the COVID-19 infection, acute transverse myelitis also has been mentioned among the neurological manifestation of the new coronavirus by several studies, but has not been extensively studied (Mao L et al. 2020, Helms et al. 2020). In a study reported by Zhao et al., acute transverse myelitis was found in a 66-year-old male patient who presented with fever and body pain, and was diagnosed with COVID-19 with polymerase chain reaction (PCR) testing and chest computed tomography (CT) scan. The authors attributed acute transverse myelitis in this patient to the cytokine storms and excessive inflammatory response. Because the patient had high levels of serum ferritin, C-reactive protein, IL-6 and SAA (Zhao K et al. 2020). Acute transverse myelitis is more likely to occur in older patients and those with comorbid diseases. Early recognition of acute transverse myelitis in COVID-19 patients is important for initiation of appropriate treatment as this condition has severe consequences.

Ataxia: Parainfectious ataxia is an autoimmune process resulting from infections aor vaccination (Overby et al. 2019). As many other neurological manifestations of SARS-CoV-2, parainfectious ataxia is also yet to be clarified, because the studies reporting ataxia developed during the course of COVID-19 are very limited. In a case report by Dijkstra et al., ataxia was found in a 44-year-old male patient diagnosed with COVID-19. Ataxia was confirmed with finger-to-nose and heel-to-shin tests in this patient (Dijkstra et al. 2020). In another case report, Povlow and Auerbach reported ataxia in a 30-year-old manle again confirmed with finger-to-nose test (Powlov and Auerbach 2020). Information about most of the COVID-related parainfectious conditions will be obtained more clearly as reports in the literature about the neurological aspects of the disease increase.

Epilepsy and COVID-19: First of all, epilepsy patients at a higher risk of COVID-19 due to immunosuppressive medications they take. Fever, which is the leading symptom in COVID-19 patients, lowers the threshold of seizures. In addition, anxiety and stress in these patients during the ongoing pandemic may trigger epilepsy seizures (Sveinsson et al. 2020). Furthermore, drug interactions between antiepileptic drugs and the experimental medications given to COVID-19 patients may be considered as another factor increasing the risk of being infected by the virus. Patients may present with seizures because of encephalitis, hypoxia, metabolic disturbances and hepatic dysfunction due to the COVID-19 infection Tonic-clonic seizures were reported in a 30-year-old female COVID-19 patient (Karimi et al. 2020). In another case report, epilepsy was reported in a 78-year-old female patient with SARS-CoV-2 (Vollono et al. 2020). Because the COVID-19 infection is associated with fever in 60 to 98% of patients, and seizure control can be challenging due to febrile diseases (Yang et al. 2020). Epilepsy itself is not a risk factor for being infected by COVID-19 virus, but immunosuppressive medications including steroids, intravenous immunoglobulins or everolimus used for the treatment of tuberous sclerosis, anxiety and stress experienced by these patients during the outbreak affect their immunity system for fighting against the disease and put epilepsy patients at a higher risk of being infected. In addition, COVID-19 has been reported to exacerbate epileptic seizures (Hogan et al. 2020).

Encephalitis: Brain imaging with CT or MRI that shows any swelling of the brain may indicate infection. Certain abnormalities on electroencephalogram (EEG) may suggest a diagnosis of encephalitis. It was reported that the first viral encephalitis case confirmed to be associated with COVID-19 occurred in a 24-year-old male patient in Japan. The patient presented with fever and then developed unconsciousness. The CSF sample was positive in this patient. Fluid-attenuated inversion recovery (FLAIR) images revealed hyperintense signals changes in the right mesial

temporal lobe and slight hippocampal atrophy was observed on the right lobe and hippocampus. These images suggested encephalitis (Morigucci et al. 2020). In addition, encephalitis was reported in a 74-year-old male patient with COVID-19 (Filatov et al. 2020).

Encephalopathy: Encephalopathy is a disease characterized by cerebral dysfunction that manifests with altered consciousness. The altered consciousness ranges from mild forms such as confusion and delirium to severe states such as deep coma. Delirium is the most common form of encephalopathies observed in patients with COVID-19. (Slooter et al. 2020). In a study by Mao et al., headache and encephalopathy were reported in 40% of COVID-19 patients, although the diagnostic criteria were not specified (Mao et al. 2020). In a retrospective study by Chen et al., it was stated that 20 of 113 COVID-19 patients developed hypoxic encephalopathy with the incidence being lower in the recovered patients (Chen et al. 2020). Like many other neurological symptoms, encephalopathy also is more common among older COVID-19 patients.

Peripheral Nervous System Manifestations of COVID-19

Hypogeusia: The neuroinvasive nature of SARS-CoV-2 may play a role in the pathophysiology of hypogeusia, also known as loss of taste. Many people with viral upper respiratory tract infections experience difficulty in perceiving flavour when eating, due to secondary rhinitis and nasal obstruction or direct viral injury to the olfactory neuroepithelium. Studies in the literature have reported that SARS-CoV-2 infection may be associated with olfactory dysfunction (ENTUK 2020). In a recent questionnaire conducted in 417 mild-to-moderate COVID-19 patients in 12 hospitals across Europe, 65.7% of the patients reported olfactory dysfunction occurring following ENT symptoms, while 11.8% of the patients stated that olfactory dysfunction occurred before any other symptoms. This result suggests that anosmia may be of value in early detection of COVID-19 (Lechien et al. 2929).

Hyposmia: The increase in threshold of detecting odours is known as hyposmia. The presence of hyposmia during the COVID-19 pandemic is an alarming sign for making a diagnostic test for the disease and for quarantine of close contacts of the patient. Numerous studies all around the world have reported sudden loss of smell and test in COVOD-19 patients, causing these symptoms to be used among the primary signs and symptoms of the disease. In a study by Nouchy et al., hyposmia was observed in 33% of COVID-19 patients and it was less common among the hospitalized patients compared to those treated on an outpatient basis (Nouchy et al. 2020). The American Academy of Otolaryngology recommends the use of loss of smell as a symptom in primary screening for the COVID-19

infection. The prevalence of hyposmia has been reported between 5.1%-98% (Mao et al. 2020, Moein et al. 2020), but the exact onset time of hyposmia has not been reported.

Guillain Barre syndrome (GBS): Respiratory involvement which is common in COVID-19 patients may be a risk factor for the development of GBS in these patients. GBS is considered the prototype of neuropathy that develops following an acute infection. Numerous cases have been reported in the literature on GBS associated with COVID-19. Zhao et al. from China reported the first GBS case in a 61-year-old female patient tested positive for COVID-19. The authors concluded that based on travel history, thrombocytopenia and lymphopenia at the time of admission may be signs of the COVID-19 infection (Zhou H et al. 2020). In addition, GBS was reported in a 54-year-old male diabetic patient from Iran (Sedaghat ve ark. 2020) and in a 54-year-old male patient from the USA (Virani et al. 2020). Both patients were tested positive for COVID-19. Toscano et al. reported GBS in five COVID-19 patients from Italy (Toscano et al. 2020).

Neuralgia: Neuralgia is among the potential neurological consequences of the COVID 19 infection. Although neuralgia has been mentioned among the other neurological manifestations, there is no study in the literature investigating the association between neuralgia and COVID-19 specifically. In a study from China, Mao et al. reported neuralgia in five patients in addition to other manifestations.

Skeletal muscle injury: In their study, Mao et al. reported skeletal muscle injury in 17 severely ill and 6 non-severe patients (Mao et al. 2020). In this study, skeletal muscle injury was defined as having myalgia and a serum level of kinase > 200 U/L. It has been reported that 11% to 48% of COVID-19 patients present with muscular pain (Wang et al. 2020). However, our knowledge on muscular involvement is limited, because of the scarcity of scientific evidence.

Conclusion

Today, we know that the COVID-19 invades the brain as many other organs and is responsible for cerebral/neurological symptoms that occur in the infected patients. Cerebral involvement is not infrequent and can lead to serious complications if not recognized and managed timely. Neurological manifestations are more likely to be seen in elderly patients and those with comorbidities and who are taking immunosuppressive drugs. Neurological manifestations caused by the novel coronaviruses involve both central and peripheral nervous systems and include disorders such as headache, dizziness, acute transverse myelitis, encephalitis, encephalopathy, hyposmia, Guillain Barre syndrome, neuralgia and skeletal muscle injury. These manifestations have serious consequences if left unrecognized and/

or untreated. Clinicians should evaluate COVID-19 patients also for the involvement of organ/organ systems other than the respiratory system. On the other hand, we lack enough and detailed information both about the exact pathophysiological mechanism through which the virus invades the brain and about the association between neurological manifestations and COVID-19. As the disease has a very dynamic and changeable course partly due to its continuous mutations, medical literature has to pursue the changing manifestation of the COVID-19 infection to adapt the management of patients.

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Chapter 38

KNEE TRAUMAS

Op. Dr. İZZET BİNGÖL[1]

1 **Ankara 29 Mayıs Devlet Hastanesi-Ortopedi ve Travmatoloji Kliniği**

Knee joint is one of the most commonly injured joints in human body, and the rate of this injury is increasing everyday due to the increase in sports - related injuries. In order to diagnose and treat knee traumas successfully, the anatomy and function of this joint should be well understood, and both of the sports injuries and emergency traumas should be well known.

ANATOMY and FUNCTION

Knee joint is the largest of the synovial joints in the body which consist of articular surfaces, menisci, ligaments, tendons, muscles, a synovial capsule, veins and nerves (1). Deep knowledge on the anatomy and function of the joint allows a rapid examination and diagnosis of the injuries. (**Figure - 1**).

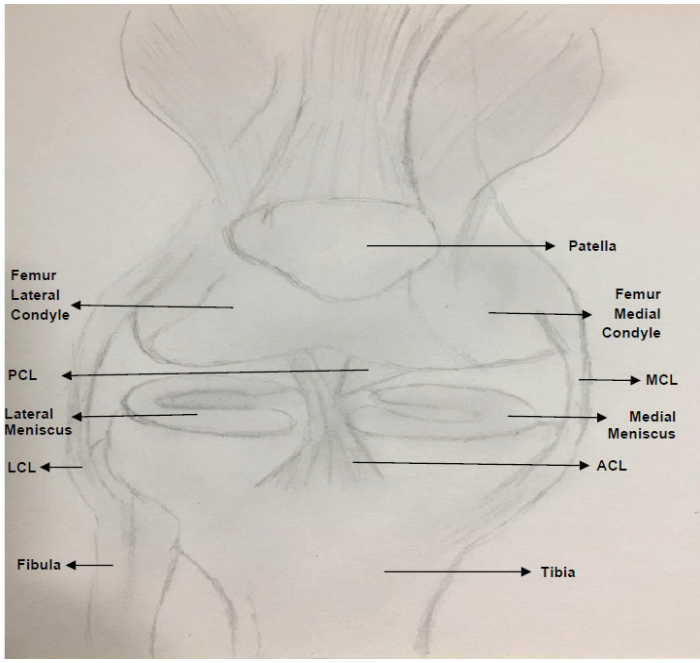

Figure -1 **:**Knee anatomy; **ACL:** Anterior Cruciate Ligament, **LCL:**Lateral Collateral Ligament, **MC**L: Medial Collateral Ligament, **PCL:** Posterior Cruciate Ligament

Bones

The joint consists of the femoral condyle and tibia plateau and patella. Fibula does not join this joint. The convex side of the knee joint belongs to the femoral condyles, and the concave side belongs to the upper end of tibia. The patella is located in the trochlear groove in front of and between the femur condyles and joins the structure of the joint (2).

In the knee joint, the harmony of the bone structures is not sufficient to provide stability. The function and stability are ensured through the

integrity of ligaments. Bone structures, capsules, meniscus and ligaments ensure the static stability in the knee joint while the muscles and tendons are responsible for dynamic stability. All these structures provide the freedom of six separate movements. Flexion and extension movements are performed around the transverse axis passing through the femoral condyles. When the knee is flexed, abduction and adduction, and the internal and external rotation movements can be performed. (2, 3).

Menisci

The incompatibility between the femoral condyles and the tibial plateau is eliminated by the meniscus in fibrocartilage structure. The menisci cover 2/3 of the peripheral part of the tibial joint surface. The cross section of the menisci is triangular and the peripheral part is thick.The proximal surfaces are concave to fit femoral condyles and the tibial surfaces are plain. There is the "Ligamentum Transversum Genu" connecting both menisciat the anterior side. While menisci contribute to the stability of the joint, they also increase the load-bearing area and reduce the load per unit area. They also have other functions such as ensuring joint lubrication, shock absorption, and nourishing the joint cartilage (2, 3). The menisci act like a proprioceptive sensory organ that protects the joint from excessive strain due to the presence of proprioceptive receptors.(3).

Cruciate Ligaments

Cruciate ligaments are of great importance in the functional anatomy of the knee. While the anterior and posterior cruciate ligament play a significant role in the anteroposterior stabilization of the knee, they also take part in the mediolateral and rotatory stability at different degrees. The cruciate ligaments are named depending on the place of attachment of eminentia intercondylaris in the tibia. Cruciate ligaments also play a role in pain and proprioception (3).

The medial (MCL) and lateral (LCL) collateral ligaments are the outer lateral ligaments that ensure the primary resistance against valgus and varus stress, respectively.

Veins - Nerves

Popliteal artery-vein and tibial and common peroneal nerves pass through the popliteal fossa. These structures are under the risk of injury during high-energy traumas, hence, the neurovascular structures at the distal to the knee should be evaluated and recorded. (4).

ANAMNESIS and PHYSICAL EXAMINATION

Case history

A detailed history should be taken and recorded during the first evaluation of the patient atthe emergency. While evaluating the knee injuries, all the previousorthopedic injuries and surgical interventions should be taken into consideration. The mechanism of injury is an important factor in evaluating the knee joint and making the final diagnosis. The direction of the trauma and the position of the knee during the trauma should be questioned. The patient should be questioned in terms of weight bearing, range of motion, localization of pain, loss of sensation, swelling after the injury and whether he/she felt or heard any noise during trauma.

Physical examination

The examination should start with a comparative inspection of the injured knee joint with the other knee joint. Whether the lengths of both legs are equal in the supine position, swelling, ecchymosis, effusion, skin integrity, mass lesion, patella location and size, muscle mass, atrophy, fistula, erythema and all pathological lesions due to trauma should be examined and recorded. If the patient can stand up by placing a weight on the knee joint, his / her gait should be evaluated.

Performing the knee examination starting from the painless area towards the painful area will minimize the patient's fear. All bone structures of the knee should be examined and local tenderness should be examined. Patella, femoral condyle and tibial plateau should be evaluated for tenderness and crepitation. Patellar palpation and ballottement tests can identify knee joint effusions. Active and passive motion range of the joint should be examined. Popliteal fossa should be checked for mass lesion, pulsation and swelling. Sensory and motor tests of the affected limb should be performed with pulses and capillary refill distal to the injury site.

RADIOLOGICAL EVALUATION

Direct radiography is the most common used imaging modalityat the emergency evaluation of knee injuries, but it may not always be diagnostic (5). Clinical decision rules have been developed to reduce unnecessary radiography requests. The most frequently used rules are Ottawa and Pittsburg Knee Rules.

Ottawa Knee Rule was first described by Stiell et al in 1995 (5). They identified 5 clinical variables that effectively ruled out a fracture in its absence, thus eliminating unnecessary direct radiography requests in the emergency department (Table-1). In the study, implementation of the rule was shown to be 100% sensitive to exclude a fracture and resulted in 28%

reduction in the use of direct radiography. Ottawa Knee Rule has been prospectively approved since then and it can also be applied for children (6). Pittsburgh Decision Rule was defined by Seaberg and Jackson in 1994 (Table-1) (7). Prospective validation of the rule revealed 100% sensitivity and 79% specificity for the diagnosis of knee fractures.

OTTAWA KNEE RESULTS	**PITTSBURGH DECISION RULES**
Age 55 or over	Blunt trauma or a fall as mechanism of injury
Isolated tenderness of the patella ;	plus either of the following:
Tenderness at the head of the fibula ;	Age younger than 12 years or older than 50
Inability to flex to 90 degrees ;	years
Inability to walk four weight-bearing steps both immediately and in the emergency department	Inability to walk four weight-bearing steps in the emergency department
Efficacy :	**Efficacy :**
Sensitivity :97%	Sensitivity : 99 %
Specificity : 27 %	Specificity : 60 %
Reduced the use of knee radiographs by 28 %	Reduced the use of knee radiographs by 52 %

Table -1: *Ottawa Knee Rule and Pittsburgh Decision Rule*

It is aimed to reduce the number of radiographs requested for the purpose of reducing costs and shorten waiting periods at the emergency departments with these rules. Although this situation has been confirmed and proven in the studies conducted, there are various applications of these rules in today's emergencies. A study conducted to identify the barriers in front of practicing these rules and non-compliance with them revealed that most physicians were aware of the rules but did not follow the rules due to patient expectations, concerns about malpractice, and the thought that a specialist might later ask for diagnosis and treatment of soft tissue injuries without fractures. (8).

Direct Radiography (X-RAY)

The first imaging method that should be requested in radiological evaluation for a patient admitted to the emergency department due to knee trauma is direct radiography. Full anterior and full lateral radiographs are required in routine practice. If necessary, additional imaging methods may be required for the definitive diagnosis.

Ultrasonography (USG)

USG is a dynamic imaging method frequently used at emergencies due to its ease of use and non-radiation emitting structure (9, 10). It can be used

to evaluate the continuity of soft tissues, muscle tears, fluid accumulation in joint structures and inflammation.

Computed Tomography (CT)

CT should be used when a fracture is suspected that cannot be visualized on direct radiographs due to the reported injury mechanism or the presence of effusion. CT is very valuable in defining the fracture anatomy and planning the operation when complex knee injuries are seen on direct radiographs (11).

Magnetic resonance (MR)

Soft tissue injuries constitute a significant portion of knee traumas among the patients admitted to the emergencies (5). MRI is a good diagnostic tool to accurately diagnose soft tissue pathologies caused by trauma and to determine the treatment method to be adopted (12). However, there are some disadvantages of MRI such as cost, time and availability which limits its use at the emergency departments. Injuries requiring immediate MRI are rare and can be requested in elective polyclinic conditions.

APPROACH TO THE PATIENT WITH KNEE INJURY

Evaluation of the patient admitted to the emergency room with knee injury should be in an algorithm (Figure - 2). After a comprehensive history and physical examination, the situation should be determined using Pittsburgh Decision Rule or Ottawa Knee Rule or direct radiography when necessary. If it is negative or if no pathology can be detected on direct radiography, the patient most probably has soft tissue injury.

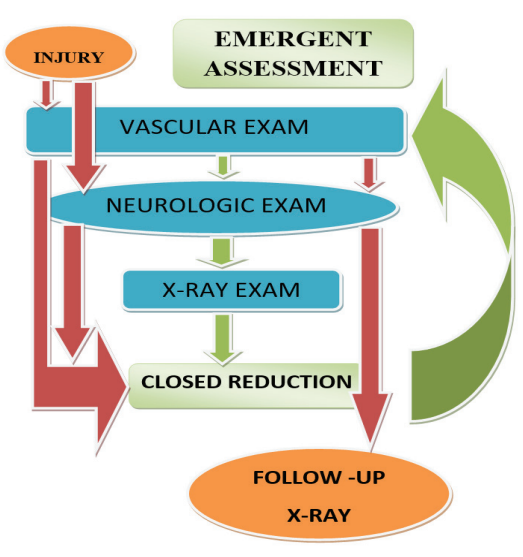

Figure - 2 :*Approach to knee injuries*

SOFT TISSUE INJURIES

The first emergent intervention at the emergencies for soft tissue injuries is partial weight loading to the extent tolerable by the patient with crutches, ice application, compression and elevation. The knee brace given to the patient for ensuring stabilization at the instable knee joint due to trauma can provide relief in the acute phase, but range of motion exercises should be given to the patient to prevent loss of motion and contracture (13,14). If the patient suffers from pain, nonsteroidal anti-inflammatory medication may be prescribed. After the necessary emergency interventions, the orthopedic outpatient clinic should be consulted for further examination and treatment.

PATELLA FRACTURES

Patella fractures constitute 1% of all fractures and are common between the ages of 20-50. Patella fracture should be taken into considered in patients who has been subjected to high-energy impact directly to the front of the knee, cannot actively open the knee after a fall, or cannot lift the knee straight (3). These patients experience pain and swelling in their knees and can generally walk. Patients with patella fractures after high-energy traumas should absolutely be examined for ipsilateral femur fracture.

Tenderness and swelling are detected on the patella. If the fracture is not displaced, the swelling may be minimal. The incisions on the patella should be investigated and an open patella fracture should not be missed. The point to be considered is the presence or absence of active knee extension. Fracture displacement of more than 3 to 4 mm is usually associated with inability to actively extend the knee because the quadriceps has largely lost its connection with the lower leg (14). The presence of active knee extension only indicates that the extensor mechanism is intact. However, if there is no active knee extension, it can be considered that both medial and lateral retinaculum is torn. If the patient is holding the lower extremity in external or internal rotation, the accompanying ipsilateral femur fracture should be investigated. This finding may be very important for a correct treatment plan especially for the unconscious patients and patients with multiple trauma.

Anteroposterior (AP), lateral and tangential patella radiographs should be requested routinely in patella fractures (Figure - 3). While lateral radiography informs about the joint surface and dissociation, AP and tangential patella radiographies illustrate a vertical fracture or an osteochondral defect clearly (15). More than half of the patella fractures are transverse fractures. Stellate-shaped or fragmented fractures are less common.

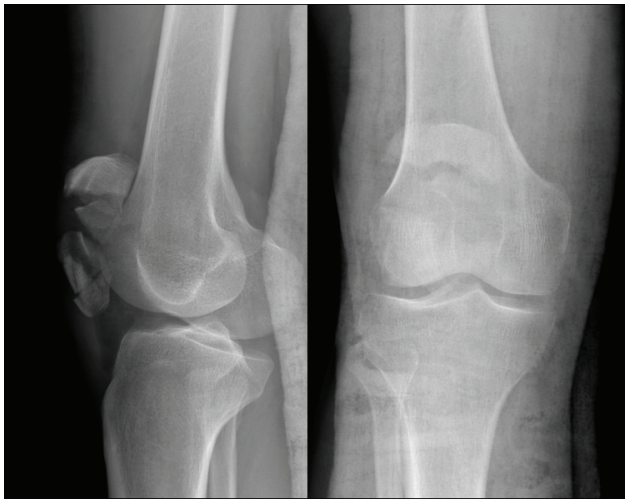

Image 1: Patella fracture (Lateral-AP Direct Radiography)

Patella may be disrupted in patella fractures that have small bone avulsions and are considered to be primarily tendon rupture. The most common osseous anomaly of the patella is the bipartite patella. An ipsilateral bipartite patella may be an old rim fracture (16).

Comparison with the unaffected knee may be required to distinguish anatomically normal variants and fractures. MRI is a useful method in insufficiency fractures, osteochondral fractures and tendon ruptures.

The aim in the treatment of patella fractures is to obtain a smooth joint surface, a complete and painless range of motion and a functional extensor mechanism (3). If the fracture has minimal displacement and the extensor mechanism is intact, the patient can be kept in a long leg plaster for 4-6 weeks (17). If the extensor mechanism is damaged or if the fracture is displaced more than 2 to 3 mm, open reduction internal fixation should be applied to the patient (17). Long leg splints should be applied to these patients until the patient is sent to the orthopedic surgeon who will perform the operation.

Patellar Sleeve Fractures

Sleeve fracture is a kind of avulsion fracture reported in children aged 8-12 years (18). Patellar tendon ruptures are extremely rare in children, and patellar sleeve fractures are the more likely diagnosis in these cases (19). It occurs with the sudden contraction of the quadriceps muscle while the knee is flexed (20). This causes the protective cartilage surrounding the patella to deteriorate and pull it downward. After a knee injury, children may apply with a high located patella as a result of rupture of the patellar tendon.

A small avulsion fracture can be seen from the lower pole of the patella on direct radiography (Figure - 4). However, the fracture line extends from the joint surface to include a relatively large part with a small bone fragment. (21).

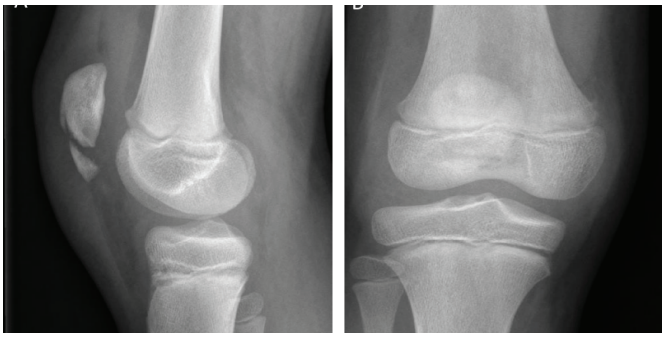

Image 2: *Patellar Sleeve Fracture(Lateral-AP Direct Radiography)*

In addition, the fracture line can extend to the medial and lateral retinaculum, causing serious damage to the extensor mechanism and is generally located at the inferior end (21). Sleeve fractures at the superior end are only a case report in the literature and are very rare.

If there is clinical suspicion of patellar sleeve fracture despite normal direct radiography, MRI should be performed (22). Identifying sleeve fractures is critical because emergency surgery is required to restore joint functions (23). Surgery may cause complications such as decreased knee flexion, ectopic bone formation or avascular necrosis. (20, 23).

TIBIA PLATO FRACTURES

In knee injuries, tibial plateau fractures may be difficult to detect at the initial evaluation and failure to diagnose may result in lifelong disability (24). Therefore, suspicion is important in the patient's history, physical examination, and direct radiographic findings, even if no fractures were detected in the first evaluation. (**Figure - 5**).

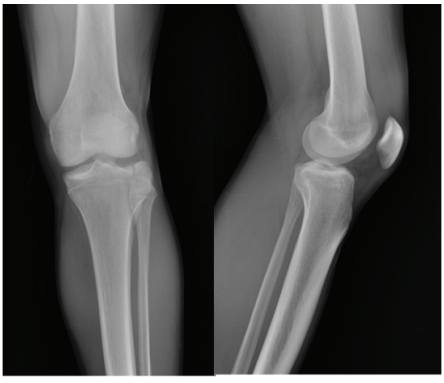

Image 3: Tibial plateau fractures (Lateral-AP Direct Radiography)

Tibial plateau fractures can occur with high-energy trauma as well as low-energy trauma. It is caused by the combination of axial, compressive load and varus or valgus force.It can be caused by a traffic accident, bumper impact, falling from a height or sports injuries. Fractures caused by high-energy trauma are mostly seen at younger ages, while those that occur with low energy are seen in older ages. The severity of the trauma and bone density determine the way the fracture breaks up and the amount of displacement. Vascular-nerve injury, severe soft tissue injury, and compartment syndrome may accompany fractures caused by high-energy trauma (25). Patients are generally unable to put weight on the affected limb.

There is usually tenderness in the proximal tibia and often accompanied by knee joint effusions. Rare complications of tibial plateau fractures; compartment syndrome and neurovascular injuries. The lower leg should be evaluated for the presence of these conditions (26). Tibial plateau fractures are often associated with ACL, PCL, MCL, and meniscal ruptures, but assessment of knee instability may be limited by pain and swelling (27).

CT examination is required in addition to anteroposterior, lateral and oblique Direct Radiographs in the evaluation of the fracture (Figure - 6). Especially the CT sections in the frontal plane show the amount of collapse in the joint very well. Due to the 10 ° posterior slope of the tibial plateau, the plateau can be evaluated better by directing the beam according to this angle while taking anteroposterior radiography. Oblique radiographs may show fracture lines not seen on anteroposterior and lateral radiographs. Traction radiographs in comminuted fractures are very valuable both in evaluating the fracture and in observing the effect of ligamentotaxis.

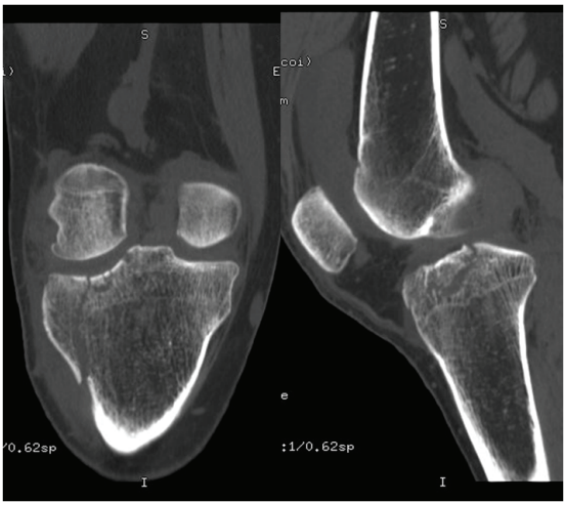

Image 4: Tibial plateau fracture (CT)

Tibial plateau fractures are most common (60%) in the lateral plateau. Bicondylar lesions occur in 25% of all tibial plateau fractures and involvement occurs at a rate of 15% in the medial plateau (28).

If there is a suspicion of fractured dislocations or vascular injury, arteriography should be performed. If distal pulses cannot be obtained in fractures occurring with high energy, arterial tension should be measured from the ankle and arm. If the ratio between the two is less than 0.9, this may be a sign of arterial injury, in this case, there is an indication for emergency angiography. Medial plateau fractures in which both plateaus fracture or dissociated as a result of high-energy trauma should be carefully examined in terms of compartment syndrome. Compartment pressure monitoring may be required in such fractures.

An orthopedic surgeon should be consulted for all tibial plateau fractures. Conservative treatment should be preferred in low-energy fractures that will not cause joint instability, do not disrupt the mechanical axis and do not cause deformity. Plaster-orthosis fixation, early movement and 8-12. After partial weight-bearing in weeks, full weight-bearing is started to the extent that the patient can tolerate. Arthroscopic surgery, external fixation or internal fixation surgery may be required for more serious injuries (29). Regardless of the treatment process, all patients may need physical therapy due to the risk of arthritis.

OSTEOCHONDRITIS DISSECANS (OCD)

Osteochondritis dissecans (OCD) is the disconnection of an osteochondral fragment from the surrounding bone and cartilage tissue. It is more common in young people and those engaged in sports. Typical patient profile is males aged 15-20 years (30). Osteochondral fracture and detachment may develop with a direct impact, as well as subchondral stress fracture may develop due to repetitive microtrauma without significant trauma, which may progress over time and cause detachment.

Crepitation, effusion, and tenderness can be detected during physical examination. Crepitation may be due to underlying cartilage damage or to the intervention of soft tissues such as fat pad, synovial plica or hypertrophic synovial tissue (31). It is possible to locate the injury by moving the joint along the arc of motion while manually applying pressure to the patella. If the patient's pain cannot be revealed with patellar pressure, it should be suspected that the pain arises from a source other than the patellofemoral joint surface (31).

Cartilage injuries occur most frequently in the distal and medial regions and are almost never seen in the upper region (32). The first step in imaging is radiographic examination. MRI may be requested in terms

of treatment plan when Direct Radiography is not adequate or OCD is suspected. MRI can perfectly show the separation of soft tissues, cartilage structure and surface defects (33).

If symptoms are not severe in young patients, conservative treatment should be tried. For conservative treatment, the fragment must be located in the crater, no sclerosis in the crater, no fluid passage indicating that the cartilage integrity is broken on MRI, and the fragment must be seen alive. If the femoral growth plate has not closed yet, good results can be expected from conservative treatment (34). However, if there is a separation in the cartilage or if the defect is large, the result is likely to be bad (35). Surgical indication arises in patients who do not respond to conservative treatment, have severe symptoms, have joint rats or have large defects. If conservative follow-up is made, the patient should be consulted with the orthopedic surgeon.

MENISCUS INJURIES

Meniscus ruptures are the most common knee injury and can occur for many reasons such as sports, trauma and discoid meniscus in all age groups. Injury that occurs during sports activities is the most common one and is generally associated with anterior cruciate ligament (ACL) rupture (36). Meniscus injuries in younger patients are usually caused by a steady foot twisting with sudden acceleration or deceleration. Degenerative ruptures are common in elderly patients and there is usually minimal or no significant trauma (37).

Patients with acute injuries typically present with pain and swelling. In mild injuries, the patient can complete his activity with increasing discomfort. Depending on the location and mobility of the ruptured part, the patient may apply to the emergency with a feeling of click while walking, a feeling of being released, and even a locked knee in flexion (38). In contrast to the effusion that usually develops within a few hours in ACL injuries, a slower effusion develops within 24 hours in meniscus injuries. Since the nerves and blood flow of the menisci are more intense in the periphery than the center, peripheral injuries cause more pain and bleeding (37).

The effusion caused by knee traumas can be assessed through inspection and palpation. If the patient has a suspicion of meniscus injury, pain may occur in medial and lateral joint line palpation. Thessaly test is the most sensitive test, which is performed by bringing the patient to flexion of the knee by 20 degrees by pressing on the extremity exposed to trauma, and then with internal and external rotation applied to the knee, evaluation of the pain, locking, clicking sound or rotation failure (37). It is necessary to apply the test on the healthy knee first to make a comparison.

McMurray test is performed by bringing the patient to supine position and forcing the foot is forced to external rotation and valgus when the knee

is flex and when the patient is forced to extension from the medial, internal rotation and varus, if there is pain or crepitation, sticking, these are the signs of lateral meniscus lesion. (39).

In Apley test, the patient lies prone (face-down) on an examination table and flexes their knee to an angle of ninety degrees. The examiner then places his or her own knee across the posterior aspect of the patient's thigh. The tibia is then compressed onto the knee joint while being externally rotated. If this maneuver produces pain, this constitutes a "positive Apley test" and damage to the meniscus is likely (38). The applicability of these tests requires experience. Therefore, the patient with suspected meniscus rupture should be evaluated as a whole and all examinations and tests should be performed.

Direct radiography is not used for the diagnosis of meniscal injuries caused by trauma. It may be requested if other etiological reasons are thought to have caused meniscus injury in the patient. It may be useful in detecting degenerative changes and injuries that may predispose patients to trauma-related meniscus injuries. Although MRI is not used routinely at emergency departments, it is the most common imaging method used for the diagnosis of meniscus injuries. The use of USG in the emergency department in knee trauma has improved, but it is not yet recommended in the routine practice (10). Orthopedic consultation is required for patients with suspected meniscus rupture.

Anterior cruciate ligament (ACL)Injuries

Nearly two-thirds of ACL injuries are non-contact injuries caused by landing towards extension during rapid deceleration, stopping or turning or jumping. Contact injuries represent about a third and result from a force or valgus strain applied anteriorly to a fixed lower leg. In both cases, the patient often reports that he hears or feels a 'pop sign' and the event is associated with severe, sudden pain (40, 41). If the patient can walk, they may complain of the feeling of falling into the void (37).

Frequent effusion can be seen during knee inspection, especially if a few hours have passed from the moment of injury. Hemarthrosis aspiration is not routinely indicated. The presence of hemarthrosis points to 72% of ACL damage (42) in diagnostic terms. In addition, the patient may experience symptomatic relief after aspiration and, accordingly, allow the examiner to perform a more accurate physical examination.

A correct ACL examination is highly accurate for injury, with a sensitivity of up to 82% and a specificity of 94% (37). The most valuable test in acute injuries is the Lachman test, which shows the forward sliding of the tibia relative to the femur when the knee is flexed at 30 degrees (43).

In addition, varus and valgus stress tests should be performed to rule out combined ligament injury. Other tests for the anterior cruciate ligament should not be applied in acute cases. The examination should be started from the knee without complaints. Both the anterior and posterior cruciate ligament play a role in the anteroposterior displacement of the knee (44). First of all, it should be ensured that the posterior cruciate ligament is intact. When it is ensured that the posterior cruciate ligament is intact, anterior cruciate ligament tests can be started. In this case, the most reliable test is the Lachman test. In the Lachman test, while the patient is flexed 25-30 degrees in the supine position, the femur is fixed with one hand and force is applied to the tibia with the other hand (45). In order for this test to be performed, the patient must be well relaxed, the femur must be stabilized very well and the patient should not have a locked knee due to the meniscus lesion. Otherwise, a false negative result will be encountered. To stabilize the femur, the physician can, if necessary, place his thigh under the patient's femur and squeeze it by hand. In the examination, both the forward sliding of the tibia with the other knee and the end point of the ligament are evaluated. The endpoint may be felt prominently or loosely or not at all. Accordingly, it can be understood that the bond is strong, semi-broken or completely broken (46). The pivot-shift test is the second test used to evaluate chronic anterior cruciate ligament ruptures. It is not suitable for acute injuries.

Posterior cruciate ligament (PCL) Injuries

The actual limiter of posterior translation of the tibia with respect to the femur is PCL (47). Patients with a PCL injury describe a direct blow to the anterior region of the tibia that pushes the tibia backward with force. Forced hyperflexion of the knee when the foot is in plantar flexion is shown as an indirect trauma mechanism (48).

Unlike ACL, PCL damage can occur even in minor traumas. Patients may complain of isolated pain in the posterior of the knee, kneeling, and pain when climbing up and down the stairs. Patients may experience a feeling of fullness in the knee joint due to effusion, and there is no feeling of instability in general. Some patients may complain of not being able to fully feel the knee joint (37, 49).

In the patient with PCL injury, physical examination is initially performed by inspecting the hip joint at 45 degrees of flexion, the knee joint at 90 degrees of flexion, and the foot on the examination table. Significant posterior displacement of the tibia due to gravity relative to the femur suggests PCL injury. With its high sensitivity (90%) and specificity (99%), the most accurate physical examination finding in detecting PCL injuries is the posterior drawer test (37). Starting the examination with a healthy joint provides important information about the patient's normal anatomy. A rapid

backward force to the anterior face of the tibia is applied, with the patient's foot fixed on the examination table. Posterior displacement of the tibia relative to the femur or the absence of a significant endpoint indicates PCL damage (40).

Medial and Lateral Collateral Ligament (MCL-LCL) Injuries

The history of trauma is of great importance in detecting collateral ligament injury. A direct impact on the lateral thigh or lower leg is the most common injury mechanism of MCL. Non-traumatic valgus stresses can damage MCL, as in an athlete who suddenly changes direction, which may cause abduction of the lower leg (50).

LCL injuries can often occur with hyperextension, rotation, and impacts to the medial side of the knee joint (40). Patients may complain of pain in the lateral region of the knee joint and instability when the leg is in full extension. (51).

Even in complete collateral ligament ruptures on inspection, a relatively small swelling may occur. Patients with LCL injuries may exhibit genu varum when standing. Tenderness may occur at the point of ligament injury by palpation of the medial and lateral areas of the joint. When examining the integrity of the collateral ligaments, the valgus and varus stress should be applied to the MCL and the LCL, respectively, with the knee flexed at 30 degrees. If the knee is fully extended and stress is applied, other structures are included in the examination. The medial opening that occurs during the stress examination in full knee joint extension suggests complete rupture of the MCL and injury to the cruciate ligaments. The lateral opening that occurs during a stress examination in full knee joint extension suggests injury to the posterolateral corner, anterior or posterior cruciate ligament as well as rupture of the LCL.

RADIOLOGICAL EVALUATION OF LIGAMENT INJURIES

Most of the ligament injuries which develop secondary to the trauma can be diagnosed with a history and a correct physical examination (38, 52, 53). Radiographs may not show damage in ligament injuries, but specific findings can also be obtained. In ACL rupture during trauma, specific bone pathologies such as Segond fracture due to stretching of the lateral capsule can be seen. In PCL rupture, lateral shifting of the tibia to the posterior and the appearance of an avulsion fracture of the PCL attachment on lateral radiography may bring rupture to the mind (48). The use of USG in the diagnosis of ACL rupture is limited, but it may be useful in identifying common hemarthrosis due to ACL rupture (54). Since the lateral ligaments of the knee joint are more superficial than the other ligaments in the joint, it is of great benefit to evaluate it by USG (10). MRI is still the most valuable imaging method in the diagnosis of ACL, PCL and lateral ligament ruptures (48).

MANAGEMENTOF LIGAMENT INJURIES

Most of the partial ligament injuries are treated with conservative treatment with physical therapy and strengthening exercises. The management of total ACL injuries depends on many factors. Surgical treatment is recommended for patients with chronic knee instability who want to continue sports that require rapid maneuvering (55). Surgical treatment is controversial, as many patients achieve successful results with conservative and physical therapy in total PCL injuries. Surgical treatment may be considered for patients who have associated avulsion fractures, who cannot heal with physical therapy, and who develop severe pain or instability (37, 40, 56). MCL is the ligament that has the greatest healing tendency in the knee, and conservative treatment is generally preferred even in cases of total rupture. LCL total ruptures are usually best managed with surgical treatment. (51).

QUADRICEPS and PATELLAR TENDON INJURIES

Extensor mechanism damage secondary to quadriceps, patellar tendon and patella trauma in the knee joint are rare injuries. Quadriceps injuries are generally seen in patients over the age of 40, patellar tendon ruptures are more commonly seen in younger patients. Quadriceps injuries are often associated with underlying degenerative diseases. Therefore, obtaining a good anamnesis is particularly important in terms of diagnosis. Systemic risk factors such as diabetes mellitus, chronic renal failure, chronic steroid use, fluoroquinolone use and connective tissue disorders may be involved in the etiology (57).

Knee extensor mechanism injuries usually occur because of sudden and severe contractions when the foot is in contact with the ground and the knee is in symphysis. While trying to prevent a sudden fall, the patient may complain of stumbling, sudden and severe pain, or a feeling of pressing in the cavity (58, 59). Tendon rupture may occur as a result of direct trauma to the patellar tendon. Patients may present with the complaints of sudden and severe pain, loss of knee joint motion and rupture sound or sensation. (57).

In the physical examination of the patients with knee extensor mechanism injury, tenderness, swelling, and especially a defect that creates a gap in the injury site can be observed (59). In the examination of patients with extensor mechanism injuries, the pathognomic findings include the inability to raise the extended leg in the supine position, the inability to extend the flexed knee, and the inability to maintain the knee in position when the knee joint is in passive extension. In total tendon rupture, it should be kept in mind that the insufficiency of knee joint extension or the prolonged duration of extension may be caused by the intact patellar retinaculum (57).

Radiological evaluation starts with direct radiographs. Patella baja total quadriceps tendon rupture, patella alta patellar tendon rupture may be seen in direct radiography findings. Insall-Savati ratio is one of the parameters that can be used in diagnosis (57). When necessary, comparative 2-way knee radiographs can be taken. USG has a significant role in diagnosing the extensor mechanism injuries and point of care use of it provides a great advantage (60, 61). MRI may be requested for suspicious cases where a definite diagnosis is not made. (58).

In extensor mechanism injuries, the knee joint is immobilized in the extension position until being evaluated by the Orthopedics. Tendon repair is required under emergency conditions. Delay in diagnosis or surgical treatment may result in retraction of the extensor mechanism, which may lead to complicated surgical intervention and poor functional clinical outcomes. If there is a suspicion of a partial rupture in the extensor mechanism, the knee joint is maintained immobile in extension position to prevent total ruptures until the orthopedic evaluation. (57, 59).

PATELLA DISLOCATION

In normal knees, there must be very severe trauma for a patella dislocation. They are relatively common injuries, especially among young athletes (62). Generally, when rotational forces are applied to the contracted quadriceps on the external pivot on the fixed leg, the medial patellar retinaculum, which is much weaker than the lateral retinaculum, forces the retinaculum and causes the patella to move laterally (Figure - 7). A direct impact to the medial or anterior patella may also cause patellar dislocation. (14).

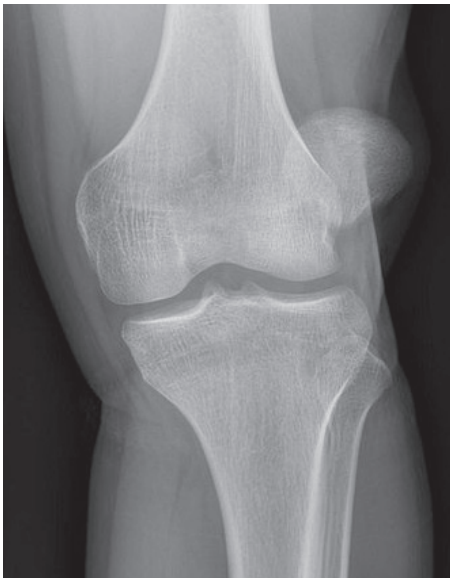

Image 5: Patella dislocation (AP Direct Radiography)

Patients usually present with sensitivity on the medial side of the patella. There is a feeling of rupture, empty and swelling in the knee. After a patellar dislocation, patients may report that they are unable to load the limb. The patient is typically unable to bend or lengthen the affected knee completely. Usually the patella is seen in an abnormal position laterally. There is often an effusion and the knee is kept in partial flexion. The patella is placed in its place either spontaneously or by the patient. Very rarely, the patella that comes to the physician with dislocation is reduced when the knee is extended and pushed medially. It can be a sign of anxiety in patients with spontaneous reduction or frequent displacement. In this test, the patient experiences pain or anxiety and the quadriceps contracts when the examiner tries to shift the patella laterally (63).

In these patients, tangential radiographs should be obtained, and if the pain does not allow this, CT should be performed. With these imaging methods, the underlying patellofemoral dysplasia can often be revealed. In acute patella dislocation, osteochondral fracture in the medial of the patella in 42% of the cases and cartilage injuries and bone contusions in the lateral femoral condyle in 75% (64). Bone contusion and retinaculum rupture can be diagnosed easily with magnetic resonance imaging. In these patients, varying degrees of patellar semi-dislocation and trochlear dysplasia are often found bilaterally (65).

After adequate analgesia, closed reduction should be performed by extending the knee joint and directing the patella medially. If this movement is not successful in reduction, the hip should be flexed in addition to knee extension. When the patella returns to its normal position, the reduction is confirmed by examination. After successful reduction, the knee should be fixed in full extension and consulted with the orthopedic clinic.

KNEE DISLOCATION

Traumatic knee dislocation is an extremely rare injury with a prevalence of less than 0.2% of all orthopedic injuries. However, its true prevalence is uncertain, as 50% spontaneously reduced due to severe ligamentous injury (66). It is a potentially threatening condition for extremities, which occurs as a result of high-energy traumas and is usually accompanied by vascular damage (67). While knee dislocations are seen as isolated injuries, diagnosis is relatively easy; In a multi-traumatic, unconscious patient, especially if spontaneous reduction has occurred; diagnosis may be delayed. This may lead to unnoticed popliteal artery injury and even loss of the extremity. In all patients with multi-trauma, knee stability should be checked, if there is instability, vascular examination should be performed and even if it is normal, it should be followed closely.

High energy traffic accidents cause 75% of knee dislocations. The remaining 25% is caused by low energy sports injuries and falls. Bilateral knee dislocation accounts for approximately 5% of all knee dislocations (66). Dislocations are classified according to the position of the tibia relative to the femur. There are five main types of dislocations; anterior, posterior, medial, lateral and rotatory (irreducible posterolateral dislocation). Approximately 40% of cases have anterior dislocation and 33% have posterior dislocation. Lateral (18%) and medial (4%) dislocations are less common (68).

In the case of knee dislocation, it can cause disarticulation due to extensive ligament damage resulting in a highly unstable knee. Generally, at least 3 of the knee ligaments have total ruptures. Combined damage of ACL, PCL, and MCL is most common (68).

An easy diagnosis is made in knee dislocation that is not reduced and spontaneously reduced due to visible deformity. If there is excessive swelling, it can make diagnosis difficult. In this case, Direct Radiography may be required. Spontaneously reduced knee dislocations are much more difficult to diagnose. It is not trivial given the possibility of neurovascular injury. Damage to the knee ligaments causes great instability, but this can be difficult to understand due to pain and swelling.

All patients with known or suspected knee dislocation should have a measured ankle-brachial index (ABI) to assess damage to the popliteal artery. An ABI greater than 0.9 has a negative predictive value close to 100% to exclude popliteal artery damage (69). An ABI of less than 0.9 requires assessment of the vascular structure. Peroneal nerve function and compartments of the lower leg should be evaluated. Peroneal nerve damage occurs in approximately one-third of all knee dislocations and manifests itself with drop foot (70).

Anteroposterior and lateral Direct Radiography should be performed in all cases with suspected knee dislocation (Figure - 8). These images confirm the diagnosis and show associated fractures. Routine use of angiography or CT angiography to evaluate the popliteal artery in cases where ABI is normal and there are no signs of ischemia is controversial (71). In recent literature studies, it has been shown that this is unnecessary in patients with palpable distal pulses and an ABI of greater than 0.9 (69, 72-74). In cases where the ABI is less than 0.9, angiography and less invasive CT angiography are acceptable methods to evaluate the popliteal artery. (75).

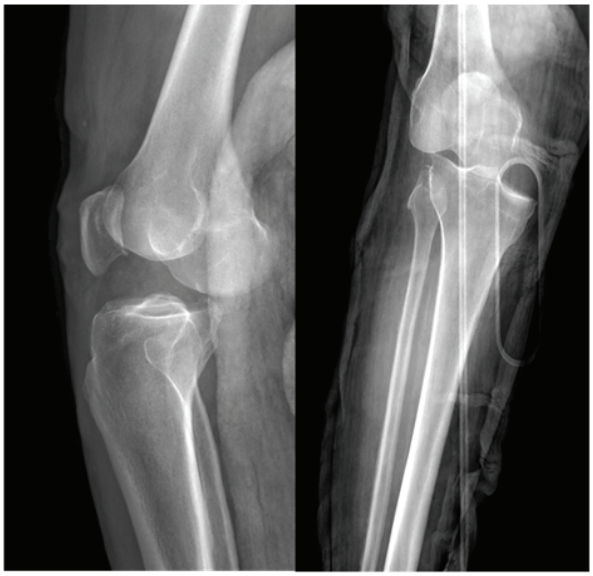

Figure - 6: Knee dislocation ((Lateral-AP Direct Radiography))

A patient with a knee dislocation injury should be treated depending on the time and location of the injury, if possible. First, advanced trauma life support protocols should be applied, and the general condition of the patient should be evaluated. First of all, the vital signs of the patient should be stabilized, and the examination for internal organ and head trauma should be performed immediately. The circulation of the limb has the second priority. If we are sure about the diagnosis of knee dislocation, reduction should be done immediately before Direct Radiographs are taken. It is reduced closed by longitudinal traction. Neurovascular evaluation should be done before and after reduction. Since knee instability continues after reduction, a temporary splint should be applied so that the knee joint is at 20 degrees of flexion.

Emergency vascular surgery consultation is required in cases where popliteal artery injury is known or suspected. Delay in artery repair can result in an increased risk of amputation. Regular vein and compartment monitoring should be done. If there is no problem in the vein and compartment angle in the follow-up of the patient, an orthopedic consultation should be requested because the structures that cause instability require surgical treatment.

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Chapter 39

LEG TRAUMAS

Vedat BİÇİCİ[1]

1 Op. Dr. Vedat Biçici Ankara Şehir Hastanesi, Ortopedi ve Travmatoloji, drvedatbicici@gmail.com

1. INTRODUCTION

The leg area is the primary support part where the body load is carried. It forms the distal femur and knee joint proximally and the ankle joint with the talus at the distal. Due to its anatomical location and structure, it is one of the body parts frequently exposed to trauma and many injuries after sports activities. After these injuries, very serious traumas, ranging from problems that can be treated with simple rest, to limb loss, can be seen. Delay in first intervention and diagnosis can cause very difficult problems to compensate. For these reasons, leg anatomy and leg traumas should be well known, so that very serious complications can be prevented with emergency interventions at the right time and in the right way.

2. ANATOMY

2.1 Bone Structures

2.1.1 Tibia

The tibia, which carries the body load, is the medial and stronger of the two bones of the leg and is the main bone that provides the leg anatomy. In terms of length and width, it takes the second place after the femur (1). By articulating the knee joint with the femur proximally, articulating with the fibula and talus, it forms the ankle joint distally. The tibia length is 30-47 cm in adult individuals, the medulla diameter is between 8-15 mm and its shape is similar to prism (2). The tibia consists of a larger upper end (tibia plateau) and a smaller lower end (plafond) and body (Figure 1).

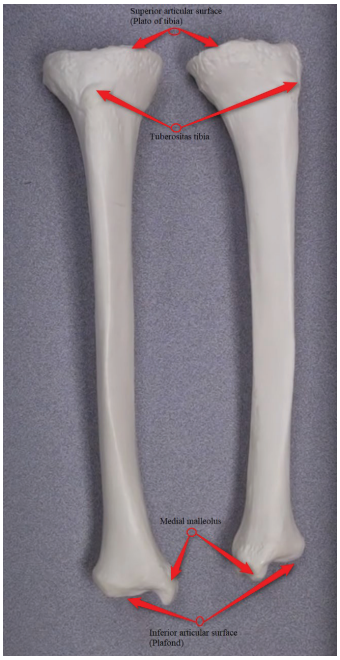

Figure 1:Tibia anatomy (Anterior and lateral view)

The upper and lower cortex of the tibia are thinner and spongious. These regions have richer blood supply. The tibia body has a thicker and non-vascular cortex and a poor vascular spongious structure. The front part covered with a thin skin layer can be felt comfortably on examination, and tuberositas tibia, the attachment site of the patellar tendon, is clearly visible. There are 2 medial and lateral condyles covered with cartilage forming a joint with the femur on the tibia plateau. In the middle of the tibia plateau, there is a relief called intercondylar eminence. The anterior cruciate ligament adheres to the anterior intercondylar area in front of the intercondylar eminence, the anterior parts of the inner and outer menisci, the posterior cruciate ligament and the posterior parts of both menisci adhere to the posterior intercondylar area behind (Figure 2).

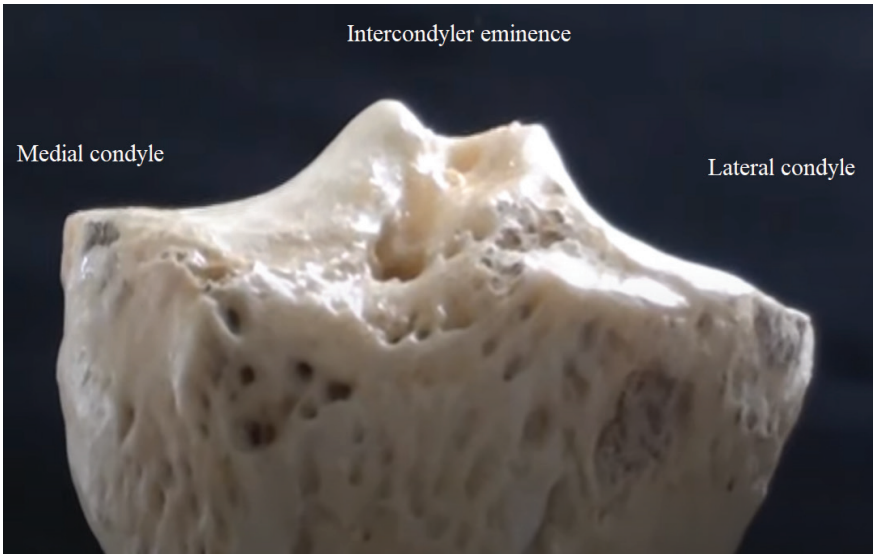

Figure 2: Anatomy of the tibia plateau

(2). The lower part of the tibia is smaller and thinner than the upper end, and wider than the tibia body. It forms the distal tibiofibular joint by articulating with the fibula from the lateral (3). The distal tibiofibular joint articulates with the talus to form the ankle joint. In this joint, the medial and posterior projections and the distal end of the fibula are called the malleolus.

2.1.2 Fibula

The fibula is a thinner bone than the tibia located on the lateral side of the leg and has no effect on load bearing. It runs in the lateral and posterior of the tibia. It consists of a wide proximal end, body and distal end (Figure 3). The posterior peroneal nerve passes posterolateral to the head of the fibula, and the lateral collateral ligament and biceps femoris muscle attach here (4). The tibia and fibula are connected by a dense membrane

between them. The distal tibiofibular joint is supported by a series of ankle syndesmosis extending from below to the intraosseous membrane.

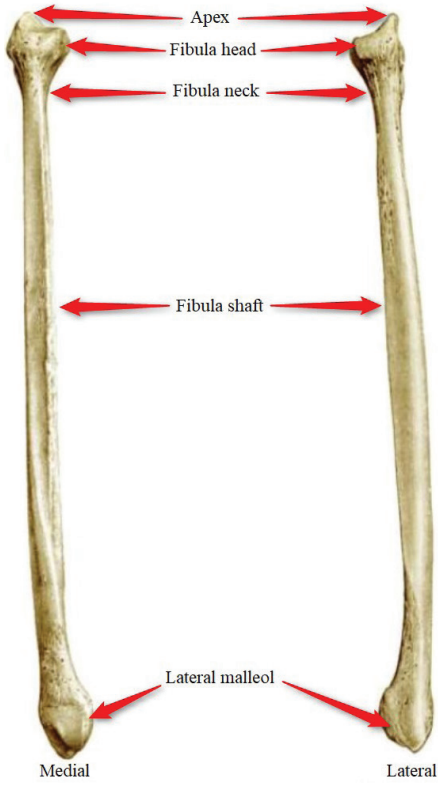

Figure 3: Fibula anatomy

2.2.1. Soft Tissue

The anatomical sections where the veins, nerves and muscles coexist with a fascia with little flexibility are called compartments. This inability to stretch the fascia is the reason for the development of compartment syndrome especially after trauma and fractures. There are four components in the leg (5). These are the anterior, lateral, superficial posterior and deep posterior compartments bounded by the tibia, fibula, interosseous membrane and leg fascia (Figure 4).

Anterior compartment: It is bounded anteriorly by the leg fascia, posteriorly by the interosseous membrane, medially by the tibia, and laterally by the fibula. Muscles in the anterior compartment are m.tibialis anterior, m. Extensor digitorum longus, m. Extensor hallucis longus, m.peroneus tertius, and these muscles are responsible for dorsiflexion of the ankle and foot. The anterior tibial artery and accompanying veins and deep peroneal nerve are in this compartment and it is the compartment that is most exposed to compartment syndrome in the body (6).

Lateral compartment: Its borders are anterior intermuscular septum in front and inside, posterior medial fibula, posterior intermuscular septum in posterior lateral, fascia in front and outside. The superficial peroneal nerve, which is responsible for the sensation of the peroneus longus and brevis muscles and the dorsal of the foot, is in this compartment (7). The muscles in this compartment are responsible for the plantar flexion and eversion of the foot.

Posterior compartment: It is surrounded by the tibia in the anterior and medial, the interosseous membrane in the anterior middle, the posterior aspect of the fibula in the anterior lateral, and the fascia in the posterior. It is divided into two as superficial and deep parts. Muscles in the superficial posterior compartment are m.gastroknemius, m.soleus and m.plantaris. The sural nerve, which is responsible for the sensation of the heel lateral, and short and long saphenous veins are in this compartment. The muscles in the deep posterior compartment are m.tibialis posterior, m.flexor digitorum longus and m.flexor hallucis longus. The posterior tibial nerve, peroneal and posterior tibial arteries are also in this compartment. The deep posterior compartment muscles provide plantar flexion of the fingers together with the plantar flexion and inversion of the foot (4).

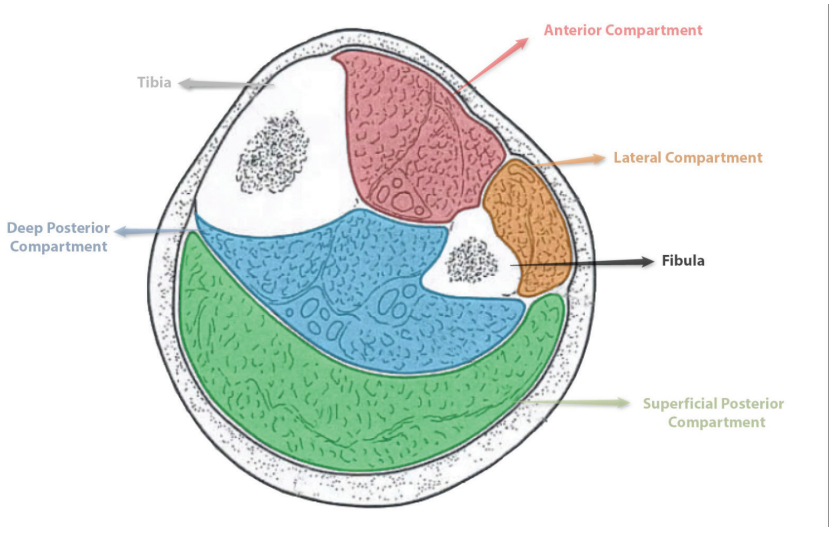

Figure 4: Leg comparments

3. Evaluation and Radiological Examinations

3.1. Story

As always in leg injuries, the history of trauma should be taken first. With this history to be taken, one can have an idea about the type of injury and other problems that may accompany. It will also facilitate the

determination of the tests to be requested to evaluate the patient. Lesions involving soft tissues (ligament and tendon injuries around the knee and ankle joint, intramuscular tears and hematoma formation) are seen in injuries during sports activities, while fractures in the leg area bones are mostly seen in high-energy injuries such as traffic accidents, occupational accidents and falling from heights. . In addition, the way the trauma occurs gives an idea about the fracture or injury site in the leg. In injuries on the vertical axis by falling perpendicular to the ground (falling from height or jumping), the spongiosa bones of the leg near the knee and ankle joints are fractured. In addition, it should be kept in mind that patients with this type of injury in their history may not only have fractures in the leg area, but also accompanying injuries or fractures in the heel, hip and spine regions related to the vector aspect of the trauma. In cases of direct trauma to the leg area (traffic accident, beating, direct impact during sports activities), there are mostly fractures in the tibia and fibula bones.

3.2. Inspection

After the evaluation made by taking a detailed history, the leg exposed to trauma should be evaluated by inspection together with the opposite extremity. The absence of muscle on the anterior surface of the tibia and its covering with a thin skin makes the injuries in this region easier to understand and there are more open fractures than other extremity fractures. Leg deformity caused by the broken tibia is easily seen. It is also necessary to detect the direction and entry points of penetrating traumas (injury with a penetrating knife or firearm) and to detect the possibility of possible vascular nerve injuries. The absence of deformity in the leg, but the presence of edema and swelling according to the opposite extremity and the localization of this edema are a warning for fractures or soft tissue damage that may be overlooked. Hematoma and swelling in the knee area should be considered in terms of tibial plateau fracture and fractures in the malleoli or tibia plateau in the ankle and are important in terms of requiring evaluation.

3.3. Physical Examination

The patient's leg should be palpated along the tibia and fibula. In this way, hematoma and crepitation can be felt in the leg. Especially, crepitation is the proof that there is a fracture in that area. However, palpation should be done carefully as patients may have severe pain. Global swelling in the leg area and the leg being very stiff on examination are a warning that requires careful attention and close monitoring for the development of compartment syndrome. Popliteal artery, dorsalis pedis and tibialis posterior pulses should be checked for circulation control. In this way, a possible vascular injury (damage to the vessels by fracture fragments, direct incision in penetrating traumas) or damage and circulation problem (circulatory arrest

or compartment syndrome as a result of mechanical compression of the fracture hematoma) can be determined and the need for urgent vascular intervention can be determined. Thus, it prevents complications that are difficult or impossible to treat in the future. In neurological examination, sensory and motor examination of the whole leg should be performed and any sensory defects should be detected. Nerves are evaluated by checking the sensation of the web between the first and second toes, the lateral heel region and the sole of the foot. Plantar flexion, dorsal flexion and eversion movements are performed on the foot to test motor functions.

After all these evaluations, if the patient is suspected of any fracture, before the patient is evaluated radiologically, the patient's fracture is reduced as much as possible by hand traction in accordance with the extremity axis in order to prevent further damage to the soft tissues and to control pain. The patient's leg is then placed in a radiolucent leg splint. Before and after the splint application, sensory, motor and circulatory examinations should be repeated and complications that may occur during splint application should be prevented. After the splint application, the extremity should be elevated above the heart level and cold application should be started and then it should be referred for radiological evaluation.

3.4. Radiological Evaluation

After the temporary fixation of the leg with a splint, anteroposterior (AP) and lateral radiographs including the knee and ankle should be taken. These radiographs are often sufficient to detect possible bone injuries and to understand the morphology of the fracture. In addition, they can be detected in radio opaque foreign bodies entering the leg area during trauma. If the patient has an injury close to or involving the ankle or knee joints, additional imaging methods are required. Especially, computed tomography (CT) is very important in the diagnosis and evaluation of spongious region fractures of the bones that cannot be seen or understood on standard graphs. In cases where standard graphies and CT are not sufficient for the evaluation of soft tissues in the leg area, superficial ultrasound (USG) and magnetic resonance imaging (MRI) can also be used. In addition, Doppler USG and CT angiography are an effective and rapid radiological diagnosis method for the detection and level of vascular injuries in the leg region.

3.5. Treatment

Wounds, soft tissue and foreign bodies should be removed and washed with saline. Simple incisions should be suitably sutured (Figure 5). In patients with open injuries, tetanus immunization should be applied if within the indication, then parenteral antibiotics should be administered to prevent the development of infection (Cefazolin 1 gr IV.). Splinting of

fractures should be done before radiological evaluations to prevent further soft tissue damage and pain control. Compartment pressure measurement should be performed in cases with excessive edema in the leg and in suspicion of compartment syndrome. In patients with compartment syndrome, the immediate treatment is fasciotomy of the affected compartment.

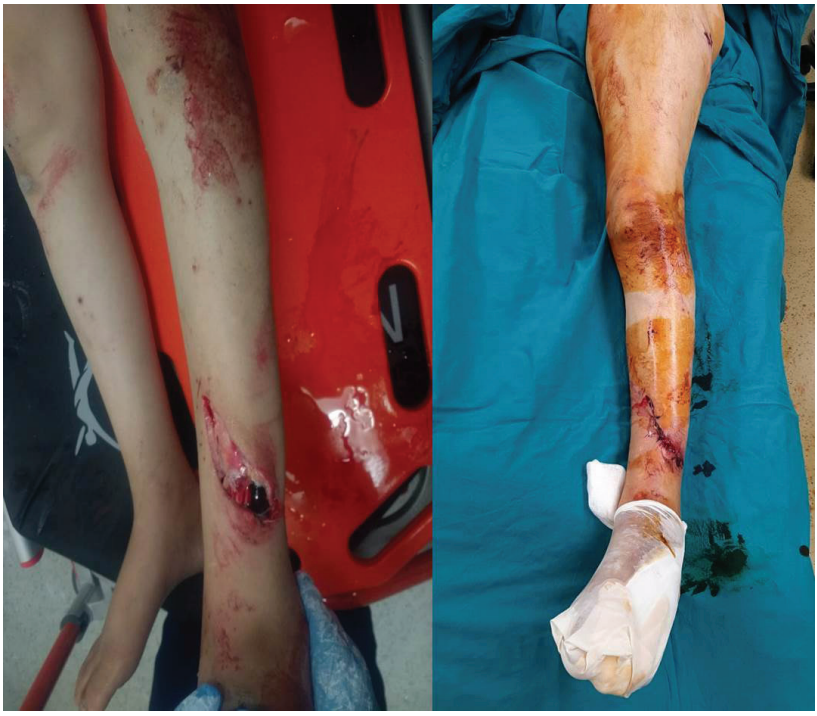

Figure 5: The appearance of open tibia fracture at the time of presentation and after the first intervention

3.6. Complications

Especially in patients with open injuries, when the wound is not cleaned well, the possibility of developing superficial or deep tissue infections increases. Being late in patients with circulatory problems can cause devastating complications ranging from treatable conditions to limb loss. Similarly, in patients with compartment syndrome, permanent disabilities may develop in case of suspicion of increased intra-tissue pressure and not diagnosed or delayed. Similarly, circulatory problems may develop even in patients with normal circulation after the splints made after the fracture are made too tightly in their dressings or the broken leg is not elevated. Therefore, the legs of the patients should be checked regularly by opening a splint if necessary and neurovascular examinations should be performed again. In the event of improper detection or reduction of fractures, healing will fail or not occur at all.

4. Leg-Specific Soft Tissue Injuries

4.1. Muscle Injuries

4.1.1. Gastrocnemius-Soleus (Calf) strain

Calf strains most often occur in the medial head of the gastrocnemius (8). This injury was first described in 1883 in relation to tennis and is often referred to as tennis leg (9). The medial gastrocnemius starts from the medial femoral condyle and crosses the knee joint and joins the lateral gastrocnemius. Then the medial and lateral gastrocnemius tendon complex is attached to the calcaneus together with the soleus muscle and joins the Achilles tendon, which makes plantar flexion of the ankle. Gastrocnemius is considered at high risk because it crosses two joints (knee and ankle) and has a high density of type two fast-twitch muscle fibers (10). Its biarthdial structure causes excessive stretching and rapid and strong contraction of type two muscle fibers. This injury mechanism can be compared to a snapping whip. The injury occurs when the ankle is in dorsiflexion and the medial gastrocnemius muscle reaches its maximum length by suddenly extending the knee. The typical patient group is tennis players or athletes between the ages of 40-60 who are active intermittently. A sharp pain and an audible "pop" sound can be heard from the back, similar to that of Achilles tendon injuries. There may be a severe pain that leaves sports activities immediately. On examination, there may be swelling and tenderness in the medial part of the calf. Pain can be revealed by passive dorsiflexion of the ankle. Standard radiographs are insufficient for diagnosis. Superficial USG and MRI provide a definitive diagnosis. In the treatment, the foot is determined to be in maximal plantar flexion. Rest, elevation and cold application reduce tissue edema and hematoma. Pain and disability can last from months to years, depending on the severity and effectiveness of the initial treatment (11).

4.2. Tendon Injuries

4.2.1. Peroneal tendon injuries

Severe dorsiflexion of the ankle in inversion may result in injury to the fibroseosis tendon sheath of the peroneal tendon. For this reason, subluxation or dislocation occurs in the tendon. Subluxation or dislocation of the tendon can be detected by eversion and dorsiflexion of the foot. Sometimes a rupture of the distal lateral aspect of the fibula can be seen on graphs. Short leg splint is made in the treatment and should be directed to orthopedics for further examination and treatment.

4.2.2. Anterior and posterior tibial tendon injury

Both are often seen in older athletes. Anterior tibial tendon rupture is less common. Patients come with middle foot pain and difficulty pushing. Requires surgical repair.

4.2.3. Achilles tendon injuries

It is the largest and strongest tendon in the human body. It is formed by the union of the tendons of the gastrocnemius and soleus muscles. It is about 15 cm in length and ends by adhering to the calcaneus. The mechanism of injury is the sudden application of eccentric force to the foot in dorsiflexion. It is often seen in male patients between the ages of 30-50 who have irregular temporary or short-term intense physical activity. Generally, rupture occurs in the part 2-6 cm above the place where the tendon attaches to the calcaneus where the blood circulation is weakest. Quinolone group antibiotic use is a risk factor for steroid injections, chronic Achilles tendinitis and Achilles tendon rupture in elderly patients. Patients can not run suddenly with a severe pain, they present with complaints of not being able to rise on the tip of their fingers and not being able to climb or climb stairs. Sometimes patients say they feel like someone has hit in the back. The snapping sound can be heard even from the outside, as in a medial gastrocnemius injury. On examination, swelling in the calf and the patient's inability to stand on the tip of the finger are observed. On palpation, discontinuity and gap in the Achilles tendon in the proximal calcaneus is detected. Specifically, the Thompson test is helpful in diagnosis (12). While the patient is lying in the prone position by bending the knee 90 degrees, the Achilles tendon, which is intact when the patient's calf is squeezed, will transmit this force and cause the foot to take the plantarflexion position. If the tendon is severed, the foot will not be able to perform the dorsiflexion movement when the calf is squeezed. However, this test may not be reliable in patients with partial rupture. Radiographs are useless for diagnosis. USG and MRI will be sufficient to make a definitive diagnosis. As a treatment, a splint or a leg cast is made in the emergency department so that the foot is in plantar flexion. Although the conservative or surgical treatment of the Achilles tendon is still controversial, surgical treatment is preferred in young active patients because the rates of rupture are lower in patients who undergo surgery (13).

Tendinitis and Tendinosis: It is often caused by excessive use and strain of the Achilles tendon. Responds to resting and appropriate physical therapy programs and non-steroidal anti-inflammatory (NSAID) treatments.

4.3. Runner's Leg Syndrome (Medial Tibial Stress Syndrome)

Runner leg syndrome, or medial tibial stress syndrome, is a severe pain condition seen on the medial surface of the tibia in people who do intense exercise or sports or have just started sports. Risk factors are runners, soldiers, people with flat soles, wrong shoe selection, and wrong training techniques (14). There is mild swelling in the leg and pain in the medial of the tibia when the finger is pressed. Periostitis of the tibia, which develops after repetitive traumas, causes this syndrome. The radiographs taken are

normal. The diagnosis is made by history and physical examination and excluding other possible causes. Compartment syndrome due to stress fracture, tendinitis and chronic exercise should be considered in the differential diagnosis. In the treatment, methods such as activity restriction, use of NSAID drugs, bandage and cold application are sufficient (15).

4.4. Chronic Exercise Induced Compartment Syndrome

Chronic exercise-induced compartment syndrome (CEICS) is an often underdiagnosed condition that causes lower extremity pain in certain at-risk populations. CEICS is most commonly seen in athletes (runners and cyclists) and soldiers without trauma. Although it is more common in adult male patients, there has been an increase in the number of studies conducted in pediatric and adolescent patient populations, especially in women. CEICS should be considered after excluding other causes of post-exertional leg pain after a comprehensive history and physical examination, but differential diagnosis should remain high on the list. The diagnosis is made by measuring the component pressure before, during and after exercise. It most often occurs in the anterior compartment of the leg. In its treatment, activity restraints, changing the footstroke pattern, physical therapy, taping and botulinum toxin A injections are applied. Fasciotomy may be required in persistent cases (16).

5. Bone Injuries Specific to the Leg

5.1. Tibia fractures

5.1.1. Tibia plateau fractures

Tibia plateau fractures are often caused by high-energy mechanisms such as traffic accidents, falling from a height, sports injury, but sometimes by low-energy traumas. While fractures occurring with high energy are mostly seen at younger ages, those occurring with low energy are seen in older ages. The severity of the trauma and bone quality determine the fragmentation of the fracture, the amount of displacement and the amount of collapse in the joint line due to the spongious bone in the tibial plateau. Post-fracture compartment syndrome, soft tissue problems, vascular and nerve injuries can occur in fractures with high energy. For this reason, it is important to consider the fracture mechanism in the patient's history (17). Anatomically, the medial plateau of the tibia is larger and solid, while the lateral plateau is smaller and higher than the medial one. Tibia lateral plateau fractures occur more frequently and are more comminuted. Medial plateau fractures of the tibia are usually in one piece, and these fractures occurring with high energy can often be accompanied by knee dislocation and knee ligament injuries (18). On examination, there are complaints of pain sensitivity in the knee area and inability to move the knee. Edema extending to the upper and middle parts of the tibia can be seen. Often

there is hemarthrosis in the knee joint. Depending on the severity of the trauma, there may be vascular or neurological complications due to the displacement of fracture fragments or due to hematoma, circulatory and neurological examination should be performed. Standard tibia 2-sided radiographs are often insufficient for diagnosis. CT is often required to fully understand fracture morphology (fracture fragments, amount of collapse in the joint). A long leg splint is applied to the patients with the knee joint at 20 degrees of flexion. Since surgical treatment is often required, tibia plateau fractures are referred to the orthopedic department for treatment.

5.1.2. Tuberositas tibia fractures

Tuberositas tibia fractures are rare fractures that are uncommon in children (19). Tuberositas tibia is the anterior and distal extension of the upper end growth plate of the tibia. The growth plate of the tuberositas tibia is more resistant to pulling forces as it has a fibrous cartilage structure until the age of 7–9, but after this age, the normal growth cartilage transforms into the colonic structure, and its resistance to pulling forces decreases. Therefore, tuberositas tibia is an injury seen in adolescents near the end of growth after sudden jumping and jumping (20). On examination, there is swelling, tenderness in the fracture area and limitation in knee extension. Diagnosis is made on lateral radiography. While a 4-6-week long leg cast applied with the knee in extension is sufficient in cases with very little fracture displacement, the treatment is surgical in other cases.

5.1.3. Tibia shaft fractures

The most common long bone fracture is tibial shaft fractures. Since the soft tissue cover on the tibia is very thin, the fracture is easily noticed and the possibility of an open fracture is much higher. Although the mechanism of fracture is learned from the patient's history, the fracture shape on the radiographs also gives clues about the injury mechanism. Transverse fractures occur as a result of trauma taken directly to the bone. Spiral or oblique fractures occur as a result of rotational trauma applied to the tibia. Multi-part fractures, on the other hand, suggest a high-energy trauma. Traumas that usually cause tibia fractures also cause fractures in the fibula through the intrarosseous membrane. Open fractures are classified by Gustillo-Anderson. Type 1 open fractures have a clean wound, minimal soft tissue contusion and an incision of 1 cm or less in the skin. In type 2 fractures, there is a skin incision larger than 1 cm without excessive soft tissue damage, flaps or avulsions. In Type 3; Open segmental tibia fracture includes amputation of vascular injury or trauma in addition to cotamine wound, fracture and tissue injury with tissue injury larger than 10 cm. The special category of type 3 fractures are gunshot injuries, contaminated open fractures due to farm accidents, and open fractures that require repair (21). The Gustillo-Anderson classification system is a prognosis indicator for

fracture healing and time to union. Soft tissue injuries, especially in open fractures, determine the emergency response plan and method. If there is no contraindication, analgesic administration is the first step. If there is an open fracture, the wound area should be washed with saline, if possible, all foreign bodies should be removed from the wound area immediately. After the wound area is dressed and sutured, leg alignment is achieved by applying traction, and then splinting with a radiolucent material to prevent further damage to the soft tissue that may occur due to the movement of bone fragments. Particular attention should be paid to the possibility of compartment syndrome in fractures with closed and delayed application period or in patients with a very tight splint or plaster. A long leg splint is applied, extending up to the hip by giving 10 degrees of flexion to the knee joint with the ankle in slight plantar flexion (Figure 6).

Figure 6: Long leg splint application after tibia fracture

Some closed fractures can be treated conservatively with a plaster cast if the cortex integrity is 50% or more, rotation deformity less than 5 degrees, lateral radiography angulation of 10-15 degrees and an angulation

of less than 10 degrees in AP radiography after reduction. Open fractures, spiral, segmental or multi-part fractures with severe edema are usually treated surgically (Figure 7). The robustness of the fibula negatively affects the reduction of the tibia and the continuity of the reduction. In patients who do not undergo surgery, fracture healing usually takes 4-5 months. Since giving weight to the broken leg accelerates the joint of the fracture, it should be started to load the leg as soon as possible. Emergency orthopedic consultation is required in open fractures. Type 1 open fractures can be treated using intramedullary nails after cleaning in operating room conditions. Type 2 and 3 open fractures are fixed with an external fixator after extensive cleaning and debridement. After wound healing and appropriate antibiotic treatment, the treatment is performed by applying 2nd stage surgery.

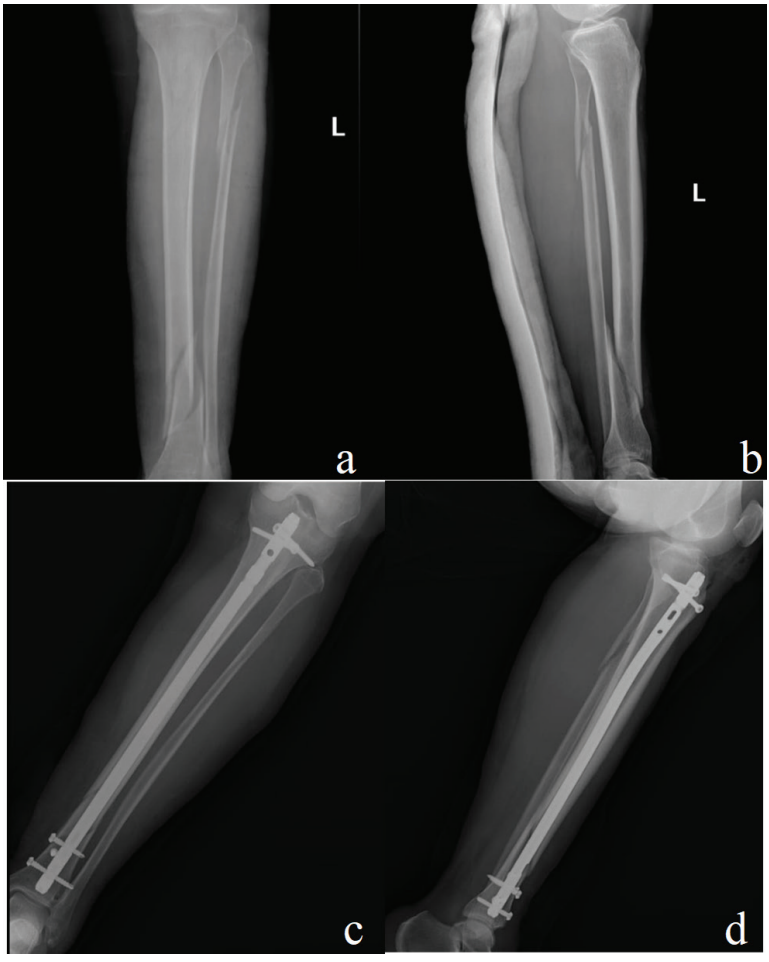

Figure 7: Preoperative (a-b) and portoperative (c-d) radiographs of the patient with oblique tibia fracture

5.1.4. Tibia plafond (pilon) fractures

Tibia pilon fractures; fractures involving the distal metaphyseal region of the tibia and the articular surface (22). Its frequency is gradually increasing due to reasons such as prolongation of life, traffic accidents, widespread sports activities, falling from height. Pilon fractures, especially in the fourth decade and more common in men, constitute 1% of all lower extremity fractures and 7-10% of all tibia fractures (23). Pilon fractures are difficult to treat because of their low incidence, the joint disintegration of the metaphyseal region and the joint due to high-energy mechanisms, and being susceptible to many complications such as chondral injuries, deep injuries and compartment syndrome (24). High energy mechanism (traffic accident, fall from height) results in extensive bone fragmentation with severe soft tissue damage. Low-energy injuries (sports activities) result in less soft tissue damage and less bone fragmentation. One or more fracture lines extending from the ankle joint surface to proximal can be seen on 2-sided ankle radiographs (Figure 8).

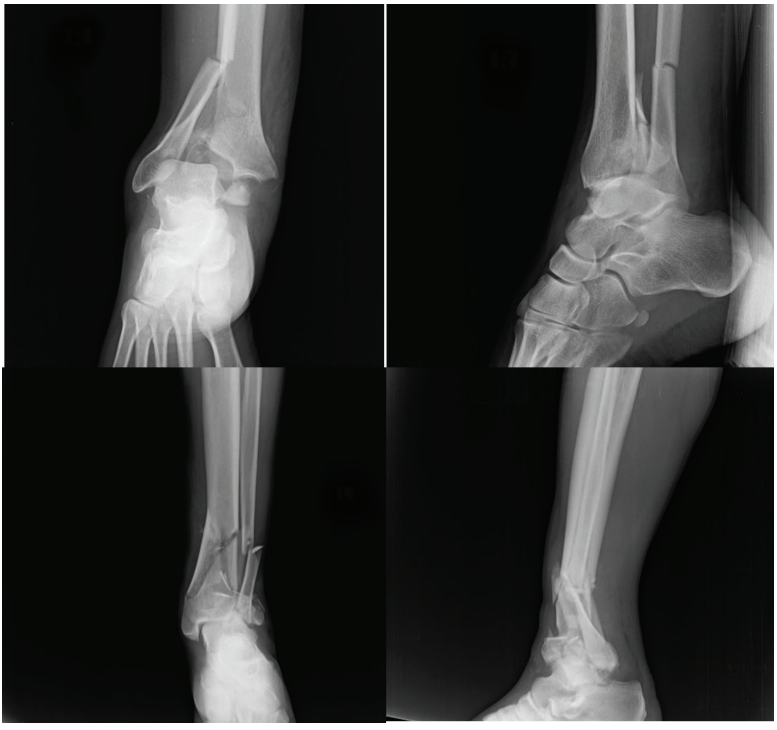

Figure 8: Ap and lateral graphs of different types of pylon fractures

After the leg traction is applied and aligment is achieved, the splint is taken. Scanning can often be done with CT afterwards. This scan will help to determine the fracture fragments and the directions of their planes, to determine the amount of collapse in the joint line of the joint damage and metaphyseal region, and to plan the treatment. Since pilon fractures are caused by axial trauma, lumbar vertebral body fractures, especially

first lumbar vertebral body fractures (Ll) can be seen. Waist examination should be performed in patients and lumbar radiographs should be evaluated carefully. In addition, compartment syndrome can easily develop, such as tibial shaft fractures. Soft tissue edema and damage after fracture determines the treatment method. Especially in patients with soft tissue damage, soft tissues are expected to heal by applying an external fixator until the actual final surgical treatment is performed (25). In this way, postoperative tissue loss and wound infection can be reduced. The main purpose of the treatment of pilon fractures is the reduction of the fracture and the best possible restoration of the joint surface. In particular, failure to restore the joint surface will increase the probability of traumatic osteoarthritis in the ankle joint in the future and will cause permanent sequelae. However, in complex fractures that are fragmented and cause bone loss, the joint surface cannot always be restored and permanent sequelae cannot be prevented (26).

5.2. Fibula Fractures

5.2.1 Proximal fibula fractures

In general, isolated fibula fractures are much less common than tibia fractures and often accompany tibia fractures. Proximal fibula fractures are seen in 2 cases. Fibular head avulsion fractures associated with lateral collateral ligament strain after trauma to the medial of the knee and a fracture in the proximal fibula (Maisonneuve fracture) as a result of external rotational force applied to the foot (Figure 9) (27).

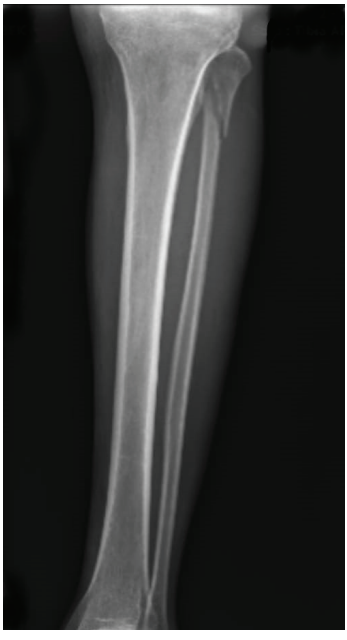

Figure 9: Maisonneuve fracture

Due to the close proximity of the fibular head to the peroneal nerve, peroneal nerve examination should be performed especially in such fractures and possible nerve damage should be determined. If there is no neurological damage, it can be treated conservatively with a splint or cast. Maisonneuve fracture creates an injury plane starting from the medial ankle with an injury such as ankle deltoid ligament rupture or medial malleolus fracture. It then leads to the rupture of the interosseous membrane (ankle diastasis) that connects the distal tibia to the fibula just above the ankle by directing upward and laterally. The last component of the injury is a proximal fibula fracture. In this type of injury, there may be a fracture in the proximal fibula, as well as in the part up to 6 cm proximal to the ankle joint. In this injury, fixation of the broken medial malleolus and the fixation of the fibula to the distal tibia as a surgical treatment provides the healing of the torn interosseous membrane (diastasis repair) (28).

5.2.2. Fibula body fractures

The fibula body area is most often fractured with the tibia. In such cases, the tibia fracture is done properly and no procedure is applied to the fibular body. When tibia aligment is achieved, the fibula body will heal on its own. However, when there is a direct blow to the fibula, there may be a fibular shaft fracture alone. The patient typically presents with pain and tenderness at the fracture site. It can be easily diagnosed on standard 2-sided radiographs. If the tibia is intact, the patient can often put weight on the leg, and can be treated with a short leg cast or brace and crutches. Patients with less severe pain can use knee stabilizer (proximal fibula) or fixation with elastic bandage, and they can press on their legs, giving the patients tolerable weight. Complete recovery is seen in about 2-3 months.

5.3. Stress fractures

Stress fractures are mostly seen in the tibia. It occurs as a result of prolonged and repetitive muscle effects on the bone that is structurally not ready for this type of injury. Stress fractures occur in two types. The first is fatigue fracture caused by the continuous application of abnormal muscle stress to a healthy bone. It can be seen in soldiers, runners running for entertainment or competition, dancers, walkers, basketball players, or anyone who engages in sports activities that require prolonged walking, running or jumping (29). The second is insufficiency fractures in the bone caused by normal muscle activities (mineral deficiency, endocrinological disorders). This type of fracture is common in older women with postmenopausal osteoporosis. However, it can be secondary to any disease that causes osteoporosis (30). Increased frequency has also been reported in patients with diabetes mellitus (DM) and rheumatoid arthritis (RA). In addition, corticosteroids are also seen in the previously operated and drilled screw holes, bone excision areas with patients using long-term

bisphosphonates. It is generally applied with the complaint of localized pain. Pain typically resolves at rest and increases with activity. In the history, while increasing the training intensity gives hints in athletes, it may even be after light exercises in the elderly. Since there is no reaction in the bone cortex in the early stage of diagnosis, it may not be detected on radiographs. The history of the patient should be taken carefully and stress fracture should be kept in mind. If there is any suspicion, MRI will be very helpful in diagnosis when there is no pathological finding on radiographs in the early period. Treatment is mostly conservative. Restriction of activity and use of plaster are sufficient. While stress fractures in the metaphyseal region heal much faster, nonunion can be seen, especially since the tibial diaphysis area has less blood supply. Cases that do not heal for more than a year are treated surgically (31).

5.4. Pediatric tibia and fibula fractures

Most pediatric tibial fractures are the result of isolated injuries. Fractures may be incomplete (torus, green tree) or complete such as adult fractures. Especially in children under 11 years of age, the majority of tibia fractures occur in oblique or spiral form in the distal 1/3 of the tibia with a torsional force (caused by the rotation of the trunk while the foot is fixed on the ground), the fracture line starts from the distal anteromedial of the bone and ends at the proximal posterolateral (Figure 10).

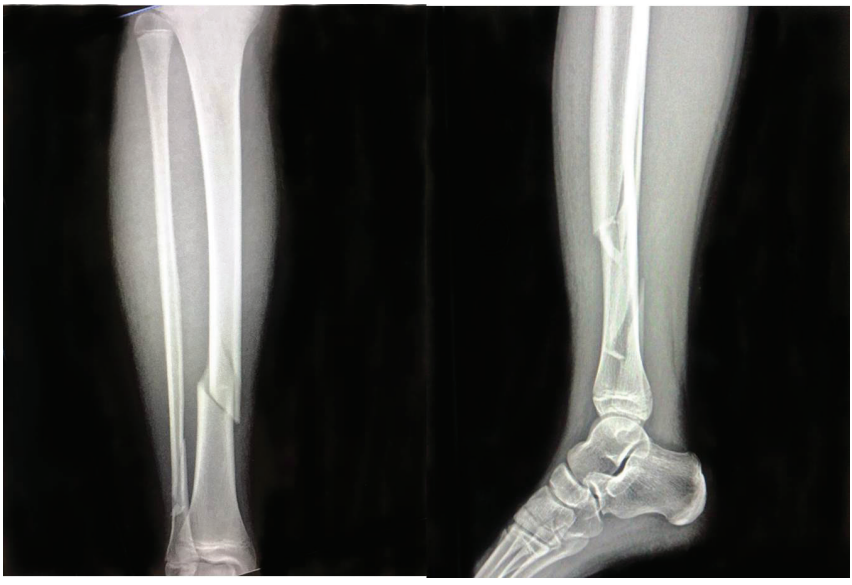

Figure 10: Ap and lateral radiography of pediatric tibia and fibula fracture

Transverse or comminuted fractures of the tibia occur with direct trauma. Transverse tibia fractures in which the fibula remains intact are rarely displaced. Approximately 30% of pediatric fractures occur with

fibula fracture (32). Isolated fracture of the fibula body is rare in children and often develops with a lateral blow to the leg. Isolated fibula fractures are usually non-separable and treated conservatively. Pain is the most obvious complaint at admission. There is swelling, sensitivity in the fracture area. It can be seen that babies and young children do not lean on their legs and do not want to walk. If there is a complete fracture, leg deformation is more evident and the fracture ends can be palpated. Neurological and circulatory examination must be performed as in adults. In radiological evaluation, ap and lateral radiographs of the knee and ankle should be taken. In rare cases, fractures may not be seen, but patients with suspicious examination and history should be treated as if they had fractures. Patients' fractures are reduced and a long leg cast is applied. Control radiographs are seen after plastering, and patients with good reduction should be followed up with a plaster cast, and orthopedics should be consulted for further investigation and treatment of non-reducible or complex fractures (33).

The approach to tibia and fibula proximal and distal end fractures is different than shaft fractures. Since the growth regions of the bones (physis line) are in the proximal and distal of the long bones, this region fractures should be evaluated carefully. Serious and difficult to treat complications such as malunion, development of deformity, and shortness of the bone may occur, especially in fractures in the physis or in the metaphyseal and epiphysis area close to the physis (34-35). Fractures of these areas should be evaluated carefully and the patient's leg should be directed to the orthopedic department after splinting.

6. Conclusion

Although the leg region has a slightly simpler anatomical structure compared to other parts and is diagnosed more easily (especially in fractures), it is inevitable that irreversible and destructive complications will occur if you are not careful. Therefore, patients should be examined and evaluated in detail. Thus acute and chronic problems that may occur in the examination and treatment of patients will be prevented.

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Chapter 40

THE BIOLOGICAL EFFECTS OF ELECTROMAGNETIC FIELDS AND INTERACTION MECHANISMS

Sevgi GÜNEŞ[1], Naci Ömer ALAYUNT[2]

1 Siirt University, Faculty of Medicine, Department of Biophysics, Center Campus, Güres Street, 56100, Siirt / Turkey, gunessevgi@yahoo.com and sevgi.gunes@siirt.edu.tr
2 Siirt University, Faculty of Medicine, Department of Biochemistry, Central Campus, Güres Street 56100, Siirt / Turkey, naci.alayunt@siirt.edu.tr

INTRODUCTION

Exposure to electromagnetic fields is increasing in today's conditions with parallel to development of technology. Sources of electromagnetic fields include radars, high-voltage lines, mobile phones, radio and television transmitters, various devices used in medical and industrial applications, microwave ovens, and electrical household appliances. Radiation can be grouped as ionizing and non-ionizing radiation according to their ability to penetrate into matter and remove electrons from the atoms or molecules that make up the object. Considering the studies reporting that these waves have harmful effects on human health, this issue becomes an important health problem.

Researches are carried out to determine the biological effects of these 50 Hz-frequency areas on the surrounding people, animals and vegetation. Using the results obtained from the researches on this subject, limit values have been brought to magnetic fields.

Today, many studies are conducted to examine the biological effect mechanism of electromagnetic fields on cell and tissue systems. Both experimental and epidemiological studies are carried out in order to determine the possible physiological and biological effects on humans, animals and plants exposed to fields with 50-60 Hz frequency for a long time.

Studies on the possible negative effects of electromagnetic fields on living things are still ongoing. Although there is a balance and some benefits of electromagnetic fields, which exist spontaneously between the Earth and living things, today there are some information and researches that exposure to EMF has adverse health effects. In this book section, we aim to draw attention to the issues that will lay the groundwork for solution proposals for limiting exposure to EMF.

Biological Effects of Electromagnetic Fields

Animal experiments and mathematical models representing human cells and tissues are carried out to determine the biological effects of electromagnetic waves on living organisms. Possible biological effects that may occur according to the results of the studies can be grouped as follows:

- Effects on cell or cell systems (effects on molecular, cellular and intracellular systems),
- Effects on genetic structure and development (mutagenic, genetic, teratological, effects on growth and development),
- Effects on tissue, cell systems and developed organ (hematological, immunological effects, effects on testicles and cardiac function, effects on nervous system and behavioral responses),

- Effects on metabolism and regulation systems (neuroendocrinological changes, effects on clinical biochemistry and metabolism) (1, 2, 3).

Biological Effects of Extremely Low Frequency Magnetic Fields (ELF MF)

There are many studies examining the biological effects of extremely low frequency magnetic fields (ELF MF). According to the studies conducted on cells and tissues exposed to low intensity electromagnetic (EM) fields for a long time;

- Synthesis of biomolecules such as DNA, RNA and protein,
- cell division,
- calcium entry-exit and binding through the membrane,
- properties of the cell surface,

It has been observed to be affected.

Accordingly, it has been found that structural changes occur in cells and tissues, hormones are affected, carbohydrate, nucleic acid and protein metabolism changes, and the immune response is affected biochemically and physiologically (4, 2).

As a result of the exposure of experimental animals (rats, mice, monkeys, guinea pigs and rabbits) to ELF-EM fields, there are findings such as a decrease in lymphocyte, leukocyte and neutrophil counts, biochemical and structural changes in the brain, and a decrease in serotonin and dopamine levels. According to the conductivity properties, the most affected tissues from those receiving ELF are cerebral fluid and blood, whereas the tissues that are affected in the second degree are eye fluid, thyroid, muscle, gastrointestinal system, prostate and testicles. ELF-MF slows down melatonin synthesis and causes disruption of sleep patterns (2,4).

According to laboratory studies, it has been determined that people exposed to ELF-EM fields have altered blood biochemistry and hematology, and changes in hormone secretion in the neuroendocrine system and digestive system. In addition to the aforementioned effects, it has been found that changes occur in the EEG wave potential in the nervous system, cause behavioral changes, the cardiovascular system, blood pressure and ECG potentials are affected, skin temperature changes, and there is an increase in DNA synthesis in fibroblasts (4).

In a study conducted in cell culture, it has been shown that the membrane potential of the cells treated with an EM field of 5 mT with a frequency of 50 Hz occurs hyperpolarization compared to the control group. However, in this study, it was reported that EM field application led to a decrease in cell number (5).

In a study conducted by Cecconi et al., It was suggested that exposure to an ELF-EM field at 1.5 mT intensity reduces the follicle capacity to reach the developmental stage, which is an important prerequisite for reproduction in pre-antral follicle culture, and thus may negatively affect female mammal reproductive potential. (6).

In the study investigating the effects of 50 Hz ELF-MF on cerebellar granule neuron apoptosis from postnatal rats, cell cultures formed from cerebellar granule neurons were exposed to MA at 300 mT for 5 days. It was observed that cerebellar granule neurons expected to undergo apoptosis under normal conditions (5.4 mM K^+) were protected from apoptosis as a result of exposure to ELF-MF (7).

While some epidemiological studies reported increased cancer risk, especially childhood leukemia and brain cancer, as a result of residential and occupational exposure to ELF-MF, some other studies have not confirmed these results (8, 9, 10, 11).

Electromagnetic Fields and Biological System Interaction Mechanisms

According to the literature reviews, the interaction mechanisms considered are grouped as follows.

1) Thermal effect (depending on temperature changes caused by fields): It is an effect that starts above 1 MHz and it is the heat energy released by the effect of resonance or spinning moment (spin moment) applied to the cells.

It increases the temperature in the living organism, affects the thermoregulatory center and biochemical reactions. Thermal effect is the conversion of EM energy to which the body is exposed to heat and an increase in body temperature. The resulting temperature increase continues until the heat is removed and balanced by the blood circulation. The temperature rise that can be caused by EM waves in the low frequency band is actually very low and can probably be easily inactivated by the body's normal mechanisms (1).

2) Non-thermal effect (associated with direct effects of electricity or MFs): **a)** effects of EM wave propagation on molecular power, molecular motion and atomic ionization, **b)** Effects of EM wave propagation on vessels and respiration (12, 13, 14).

The photon energies of low frequency EM waves are not at a level that can ionize atoms and molecules. As a result of being affected by non-ionizing EM waves in the environment, thermal and non-thermal effects may occur in living organisms (13).

Depending on the increase in frequency, the depth of energy penetration decreases. Most of the energy from EM fields in regions close

to the surface is absorbed. Low frequencies can reach much deeper than high frequencies. Therefore, low frequency EM waves affect deeply anatomically located tissues more. In line with these explanations, it can be said that while the harmful effects of high frequency MFs affect the superficial tissues more, low frequency MFs affect the deep tissues of the organism (3).

Literature Review on the Effect Mechanisms of Electromagnetic Fields

In recent years, the effects of non-ionizing EM fields on biological systems have been examined by many researchers and their mechanism of action has been explained. Some of these studies reported that the EM field effect on the biological system is through the increase in reactive oxygen species (ROS). Free radicals can be produced as intermediates in metabolism and affect lipid, protein and DNA. Thus, any increase in free radical production can increase the rate of chemical damage in DNA.

One of the most important free radicals is superoxide radical (O_2) originating from mitochondria, hydrogen peroxide (H_2O_2) formed by SOD activation, and peroxynitrite ($ONOO^-$), which consists of superoxide and nitric oxide (NO).

These continuously produced radicals are detoxified by SOD, glutathione peroxidase (GSH-Px) and catalase (CAT). Excessive free radical production results in antioxidant consumption and the defense mechanism is insufficient. Disruption of the oxidant / antioxidant balance in the cell results in damage to cellular molecules such as lipid, nucleic acid and protein (15, 16, 17, 18).

In a study conducted by Goraca et al., Antioxidant capacity and ROS formation were investigated in blood samples and heart tissue taken from rats exposed to MF with 40 Hz frequency and 7 mT intensity for 14 days (30 and 60 minutes a day). As a result of the study, it was determined that MF affects the antioxidant defense of the organism as well as ROS production in the heart tissue and creates oxidative stress in the heart tissue. In addition, according to the study findings, it was shown that the effect of ELF-MF on oxidative stress parameters is dependent on the application time (19). Free radicals are produced as intermediates in metabolism and they can affect lipid, protein and DNA. Thus, any increase in free radical production can increase the rate of chemical damage in DNA (20).

In addition, it has been reported that short-term exposure to EM fields may cause an increase in free radical production as well as affect intracellular calcium concentration and transmission (21, 22).

Muscle fibers continuously produce both ROS and nitric oxide (NO) (Figure 1). It is known that many of the cellular functions in skeletal muscle

are modulated by ROS and NO. These cellular functions; It is also reported to play an important role in the regulation of glucose uptake, mitochondrial metabolism, gene transcription, muscle catabolism and contraction. Evidence shows that muscle-derived ROS and NO have complex autocrine / paracrine effects on cellular components that regulate contraction (23).

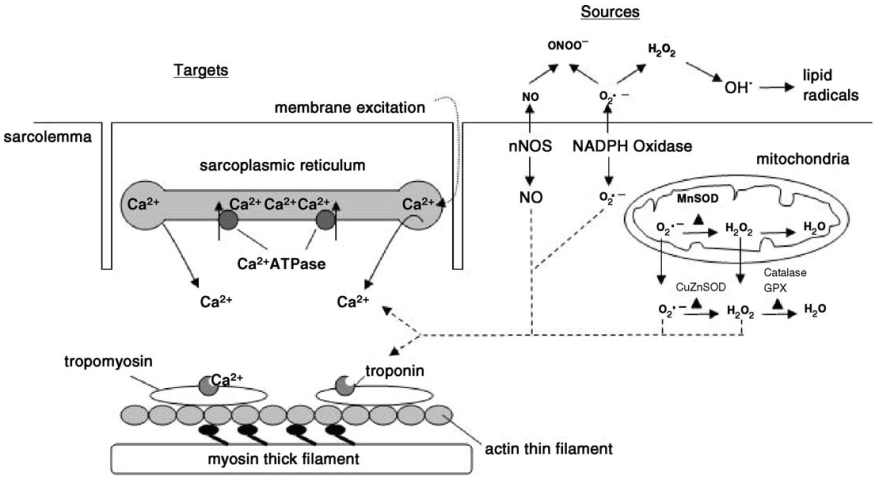

Figure 1. *Sources of free radicals in muscle.* **Abbreviations:** *ONOO (peroxynitrite), H_2O_2 (hydrogen peroxide), H_2O (water), $O_2^{\bullet-}$ (superoxide anion), $OH^{\bullet}$ (hydroxyl radical), NO (nitric oxide), MnSOD (manganese superoxide dismutase), CuZnSOD (copper - zinc superoxide dismutase), GPX (glutathione peroxidase), Ca^{+2} (calcium) (from Smith et al. 2006) (23).*

Supinski reported that free radicals can affect and alter the function of many intracellular-biophysical processes (sarcolemmal AP dissemination, sarcoplasmic reticulum calcium use, mitochondrial function, contractile protein interactions) and cause changes in the force-generating capacity of the muscle (24).

In a study conducted in muscle cell culture, the responses of a single muscle cell as a result of short-term exposure to ELF-EM field were tried to be determined by single cell confocal microscopy technique (25). In this study, C2C12 muscle cells, an in vitro model of the skeletal muscle cell phenotype, were used. As a result of the exposure of myoblast and myotube cells to an ELF-EM field at 0.1 mT intensity for 30 minutes, there was no significant difference in ROS, while a significant increase was observed in H_2O_2 production when exposed to 1 mT intensity, and no difference in $O_2^{\bullet-}$ levels. Qualitatively and quantitatively similar results were obtained in myotube cells. As a result, ELF-EM field exposure a) increases ROS production in myoblasts and myotubes in parallel with the decrease in mitochondrial membrane potential, b) activates the cellular detoxification system with an increase in catalase and glutathione peroxidase activity,

and c) intracellular Ca^{+2} channels are an agonist (caffeine) or a depolarizing agent (KCl), it has been reported to change the intracellular Ca^{2+} balance by increasing cellular reactivity and spontaneous activity in myotubes (25).

In the past years, many studies have been conducted stating that ELF-MFs can cause tumor formation. Studies conducted at the same time determined the role of apoptosis in the tumor process. These results directed the researchers to examine the effects of MF on apoptosis. Although there are some differences, in the literatures (26) that apply different experimental protocols as a whole, it is stated that there are changes in the apoptosis process of the cells exposed to MF. In addition, these studies have reported that the role of Ca^{+2} ions in the apoptotic process is important (26) and the amount of Ca^{+2} increases as a result of static MF exposure (19). Static and 50 Hz frequency magnetic fields stimulate many processes in cells:

- In vitro studies in mammalian cells inhibit proliferation ability (27),
- Increases mutation in cells exposed to different mutagenic substances (28,29),
- It increases the survival rate of tumor cells after treatments that cause cell death (30),
- It increases the tumor rate in mice affected by cancer (31),
- It affects neoplastic development by changing the expression of cancer-related genes (32).

In a study using sinusoidal MF (50 Hz frequency), it was suggested that free radical metabolism was affected and this effect was achieved through the immune system according to the findings of the study (33). Oxidative stress may be the result of increased free radical production and decreased antioxidant defense. Therefore, investigation of antioxidant consumption as an oxidative stress biomarker is possible by evaluating the decrease in antioxidant amounts or the increase in their metabolites.

Marchionni et al. (34) showed that MF exposure at 50 Hz, 125 μT in rat DRG cell culture increased Ca^{+2} channel functionality and parallel to this, the open time of K^+ channels activated by Ca^{+2} could increase. In a study examining muscle mechanical properties, a significant decrease in muscle concussion strength was observed as a result of chronic exposure to MF, and this finding was attributed to the effect of MF to increase Ca^{2+} ATPase activity. These study results suggest that MF exposure may alter ATPase activities, thus altering the bioelectrical and biomechanical properties of the rat diaphragm muscle (35). According to the results of the study in which the effects of 50 Hz-frequency sinusoidal (5 min. Open / 10 min. Off, 1 mT) MF on cell cultures created by taking biopsy from skin

diploid fibroblasts, it was found that it had no effect on intracellular Ca^{+2} in human fibroblast cells (36).

It was found that oxygen consumption and ATP production were not affected by applying MF at 2 mT for 2 hours on cortical synaptosome cultures isolated from Sprague-Dawley rat brains (37). In a study in which snail brains were exposed to 10 mT static MF, it was found that Na^{+} -K^{+} ATPase activity increased two times. In the same study, it was determined that after exposure to static MF, the duration of AP was shortened compared to the control, and interspike intervals were prolonged. It has been suggested that the increase in Na^{+} -K^{+} pump activity as a result of being affected by static MF may cause a decrease in intracellular Ca^{+2}, which maintains the burst rhythm in brain neurons (38). This result is important in terms of showing that static MF affects neuronal membranes.

In a study, it was shown that both supplemental and ambient MFs modulate myogenesis by stimulating transient receptor potential-C1-mediated calcium entry (39). In the study conducted by Duncan and Dinev in 2019, it is suggested that high-intensity focused electromagnetic field technology increases muscle thickness and hypertrophy (40).

Chronic exposure to ELF-EMF (50 Hz, 1.5 mT and for 7 months) was found to have no effect on the histological structure and mechanical activity of the rat diaphragm muscle, but caused partial changes in some bioelectric activity parameters (41).

Jankowska et al. in their study conducted at 2015, it was found that exposure to ELF-EMF (0.7 mT) reduced the discharges recorded from cercal axons. This clearly shows that the function of mechanosensory neurons is impaired by the effect of ELF-EMF. It is suggested that these effects are seen as evidence that electromagnetic fields can change basic electrical neuronal membrane properties.

CONCLUSION

When the literature is examined, in the studies conducted by different groups, the severity, frequency, application time of MF, the type of tissue exposed to MF, etc. It was seen that the parameters were very different and it was impression that these parameters could affect the results.

It is seen that the obtained effects are analyzed with different methods. For these reasons, it is not possible to compare the results and show clear results. It is concluded that many more studies should be conducted in vitro and in vivo.

It was concluded that a statistical meta-analysis that evaluates the studies carried out so far on this subject should be done and the results should be examined together.

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Chapter 41

THE EFFECT OF HONEY ON ORAL MUCOSITIS IN PATIENTS WITH HEAD AND NECK CANCER RECEIVING RADIOTHERAPY: A LITERATURE REVIEW

Gül Güneş AKTAN[1], Ebru BAYSAL[2]

1 Gül Güneş AKTAN, Araştırma Görevlisi, Ege Üniversitesi Hemşirelik Fakültesi Hemşirelik Esasları AD
2 Ebru BAYSAL, Araştırma Görevlisi Doktor, Manisa Celal Bayar Üniversitesi Sağlık Bilimleri Fakültesi Hemşirelik Esasları AD

INTRODUCTION

Most head and neck cancers arise from the squamous cells that comprise the mucosal surfaces of the head and neck area. In addition to surgery, external radiation therapy (RT) is used alone or in combination with chemotherapy in its treatment (Cady and Jackowski, 2014). During and after cancer treatment, some oral cavity complications such as oral mucositis (OM), dry mouth and dysphagia occur frequently (Mercadante et al., 2015). Symptoms are usually seen during the six-week RT and are corrected in the eight weeks following the completion of the treatment. The severity of the symptom, diagnosis, treatment, duration of treatment, daily dose of radiation, individual patient characteristics, mouth hygiene and the existence of comorbidities depend on several factors (Charalambous et al., 2018).

OM is an inevitable side effect observed in most patients with head and neck cancer receiving RT. It is seen in 80% of patients (Alvi et al., 2013; Rao et al., 2017). Radiation-induced oral mucositis may occur in the oral, pharyngeal and laryngeal mucosa between the 2nd and 3rd weeks of conventional RT as a result of ionized radiation exposure (Charalambous et al., 2018; Mercadante et al., 2015). The painful state caused by OM in the mucosa may require the use of strong opioid analgesics generally leading to difficulty in eating, drinking and swallowing, which causes weight loss (Cho et al., 2015).

OM may occur in varying degrees of severity. It is classified as tolerable (grade 1 and 2 mucositis) and intolerable mucositis (grade 3 and 4) based on its severity (Rao et al., 2017). Severe OM leads to mouth ulcers, painful dysphasia, parenteral nutrition requirement, increase in the risk of mucosal and systemic infection, extended hospital stay times, tapering of treatment and causing therefore quality of life to decrease (Carulli et al., 2013; Mercadante et al., 2015).

The clinical practice guidelines developed for the prevention and treatment of OM by experts of the Multinational Association for Supportive Care in Cancer (MASCC) and The International Society of Oral Oncology (ISOO) recommend the use of mouth care protocols (Evidence Level II) (Lalla et al., 2014). Although a great variety of local and systemic methods (antiseptic solutions, vitamin E-A, growth factors etc.) are available for the prevention and treatment of OM, none of the existing methods are capable of preventing standard, effective and secondary side effects (Charalambous et al., 2018). This frequently causes to turn to complementary and alternative therapies (CAM) in addition to medical treatment for the prevention and treatment of OM in cancer patients (Osmanoglu Yurdakul and Esenay, 2019).

Throughout history, honey has been used for treating burns, surgical wounds and oral infections due to its antibacterial, pain killing, antioxidant and epithelization-enhancing medical properties (Charalambous et al.,

2018; Osmanoglu Yurdakul and Esenay, 2019). These properties of honey as well as its low cost has made it a potentially attractive therapy for the prevention and treatment of OM (Alam et al., 2014; Charalambous et al., 2018; Friend et al., 2018). In studies carried out with cancer patients in recent years, honey has been found to reduce pain in the mucosa, delay the generation, decrease the severity and contribute to the healing of OM, as well as preventing weight loss (Charalambous et al., 2018; Co et al., 2016; Jayachandran and Balaji, 2012; Khanal et al., 2010).

The related literature suggests that evidence-based CAM practices in patients with head and neck cancer receiving RT would have a preventive effect on many complications, particularly OM, increase patients' quality of life and reduce health care costs. The present literature review aimed to examine the effect of honey on the prevention of OM in patients with head and neck cancers receiving RT.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

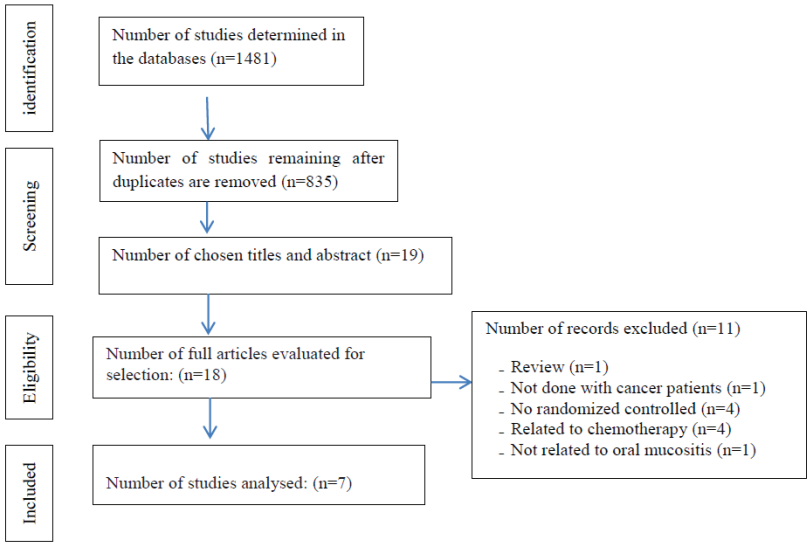
The present review included all the studies conducted between the years 2000 and 2019 concerning the effect of honey on the prevention of OM in patients with head and neck cancers receiving RT. The related articles were reached through research on electronic access systems and the data bases "Ebscohost", "Pubmed", "Science Direct", "Scopus", "Google Scholar" and "Medline". Recurring publications were eliminated using the Mendeley program. The literature review was carried out in the Septemper-November 2019 period using the keywords "honey" AND "oral mucositis" AND "head and neck cancer" AND "radiotherapy". Out of the total 1481 articles reached as the end of the review, 7 articles meeting the required criteria were included for evaluation.

Inclusion Criteria

The present literature review included randomized controlled studies which were published in full text in English. Studies conducted on animals and the grey literature were excluded. The target sample consisted of patients with head and neck cancer who were over the age of 18 and receiving RT. Articles published between 01/01/2000 and 31/12/2019 were included in the review.

Study Selection

Full titles and the abstracts of the articles reach in the first review were evaluated by two authors in terms of their conformance with the eligibility criteria. Articled failing to meet the eligibility criteria and the recurring ones were excluded from the review. Full texts of the remaining articles were assessed for conformance (Flow chart).



Data Collection

Related data (article title, author information, country where the study was conducted, study design, the type of honey used, OM evaluation scale used in the study endpoints, main results and tapering of treatment due to honey) were obtained from studies which were examined using a standard data extraction form. In line with this form, studies were reviewed and evaluated by two researchers separately. Finally, studies evaluated by both researchers were combined in a single form. The studies were evaluated for methodological quality using Jadad scale (Halpern and Douglas, 2007)(Table 1).

RESULTS

In the first literature review, 1481 article titles were reached: Ebscohost (48), Pubmed (15), Science Direct (84), Scopus (22), Google Scholar (1300) and Medline (12). As seen in Figure 1, most of the articles were excluded as they failed to meet the eligibility criteria (Figure 1). Studies concerning the use of honey in patients with head and neck cancer receiving RT treatment are summarized in Table 1. All of 18 articles meeting the criteria according to their titles and abstracts were read in full texts. Only 7 of these articles were found to meet the inclusion criteria. When the studies included in the review were examined, it was seen that the effects of honey implementation were compared to 0.9% saline, 0.15% benzydamine hydrochloride and lignocaine gel. The honey types used were seen to be traditional types obtained from such extracts as thyme, ziziphus and astragale.

It was also found that four of the studies used Radiation Therapy Oncology Group (RTOG) Grading System to evaluate the patients' OM

levels, two of them used WHO Oral Mucositis Grading System while one used Oral Mucositis Assessing Scale (OMAS). The studies reviewed have shown that honey is effective on the degree of OM (n=7), weight maintenance (n=4), pain (n=2), quality of life (n=1), oral activities (n=1), OM initiation day (n=1), total duration of OM (n=1) and OM healing (n=1). It was seen that no studies reported any state that would cause to stop the application of honey. Compared with all products used in control groups, honey was found to be superior in all independent variables (Table 1).

Table 1. Summary of randomized trials on honey and oral mucositis

First author/ year/Jadad	Country	Sample	Type of honey	OM Assessment Tool	Endpoints OM	Main Results
Charalambous 2018 Jadad score: 3	Cyprus	72 patients Group 1: 36 patients / with 20 ml of thyme honey in 100 ml water / gargling in the mouth/ 15 minute before and after RT and six hours later, three times a day for seven weeks (starting from the first day of the 4th week of radiotherapy). Group 2: 36 patients / with saline %0.9 (RT: Total dose of between 50 and 60 Gy)	Thyme	OM grading scale adapted by the RTOG	• Weight loss • OM grade • Life quality • Oral activities and preblems (i.e. mouth and throat pain, eating swallowing and drinking)	In the experimental group; • Lower OM grades (p <0.001) • Good body weight (p < .001) • Healing in overall health(p <0.001) • Increase in quality of life (p < 0.001) • Study was not discontinue due to honey
Amanat 2017 Jadad score:3	Pakistan	82 patients Group 1: 41 patients / with 20ml ziziphus honey / 15 minute before,15 minute after the RT Group 2: 25 patients / with saline 0.9 % (RT:Total dose of between 60 and 78 Gy in 4–6 weeks)	Ziziphus	RTOG Grading System.	• OM grade	In the experimental group; • Lower grades of OM (p <0.032) • Study was not discontinue due to honey
Alvi 2013 Jadad score:2	Pakistan	60 patients Group 1: 30 patients/ with 20ml pure honey/ 15 minute before, 15 minute, 6 hours after RT Group 2: 30 patients / with 20ml saline 0.9% / rinsing mouth (RT: 2 Gy per day five times a week up to the dose of 66Gy)	Pure natural honey	WHO OM grading system	• weight loss • OM grade	In the experimental group; • Lower OM grades (p=0.039) • Healthier body weight (p=0.002) • Study was not discontinue due to honey

First author/ year/Jadad	Country	Sample	Type of honey	OM Assessment Tool	Endpoints OM	Main Results
Khanal 2010 Jadad score:2	India	40 patients Group 1: 20 patients / with 20ml honey / 15 minute before,15 min after the RT, once before going to bed. Group 2: 20 patients/ with lignocaine gel (RT:with a total dose of 6000 cGy in 6 weeks / once a day, for five days a week).	Bee honey	RTOG mucositis assessment scale	• Grade of OM • Pain due to OM	In the experimental group; • Lower OM grades (p< 0.0001) • Less pain • Study was not discontinue due to honey
Jayachandran 2012 Jadad score:2	India	40 patients Group 1:20 patients/ with 20ml honey /15 minute before and after RT, six hours after RT. Group 2: 20 patients/ 15ml 0.15% Benzydamine hydrochloride/ 15 minute before and after RT, six hours after RT Group 3: 20 patients/ 20ml 0.9% normal saline/ 15 min before and after RT, six hours after RT. (RT:Total dose of 2 Gy per day five times a week up to 60–70 Gy a period of 6–7 weeks).	Dabur honey	WHO OM grading system	• OM grade • OM onset day • Recovery of OM	In the experimental group; • The delayed onset of OM (p<0.001) • After the end of RT fast recovery • Lower grade of OM during RT • Study was not discontinue due to honey
Motallebnejad 2008 Jadad score:2	Iranian	40 patients Group 1:20 patients/with 20ml honey /15min. before and after RT then 6 hours after RT. Group 2:20 patients/ with 20ml saline 0.9%/ before and after each RT session. (RT:with a total dose of between 50 and 60 Gy in five to six weeks).	Honey from Thymus and Astragale	OMAS	• Weight loss • OM grade	In the experimental group; • Lower OM grades (p< 0.0001) • Good body weight (p< 0.001)
Biswal 2003 Jadad score:2	Malaysia	40 patients Group 1: 20 patients/ with 20ml honey /15 minute before and after radiation therapy,20ml after 6hours RT. Group 2: 20 patients/ with 20ml saline 0.9%/ before and after each RT session. (RT:dose rate of 2 Gy per day five times a week up to a dose of 60–70 Gy a total period of 6–7 weeks).	Nectar from tea plant (Camellia sinensis)	RTOG Grading System.	• Weight loss • OM grade • Total duration of OM	In the experimental group; • Lower grades of OM -grade 3/4 mucositis- (p<0.0001) • Good body weight (p <0.05) • Study was not discontinue due to honey • Not significant mean total duration of OM

DISCUSSION

In the review of the related literature, only seven randomized controlled studies were found evaluating the effects of honey in the prevention of OM in patients with head and neck cancer receiving RT. Due to its high viscosity, acidic pH, hydrogen peroxide production at noncytotoxic levels, high osmolarity, enzymes with growth factor and rich nourishing properties, honey can inhibit bacteria growth and accelerate healing (Biswal et al., 2003; Jayachandran and Balaji, 2012; Motallebnejad et al., 2008). In the global literature, it is seen that honey obtained from different geographical locations and different extracts are used in the treatment of different health problems such as wounds, burns and oral infections (Hawley et al., 2014; Jull et al., 2015; Münstedt and Männle, 2019). Two of the studies were conducted in Pakistan, two in India, one in Cyprus, one in Iran and one in Malaysia. In the studies reviewed, traditional natural honey types obtained from extracts like thyme, ziziphus, astragale and dabur honey were used. It should be remembered that the effect of honey is not solely based on its antibacterial effects or geographical location and pollen source, but also on the combination of all the healthful properties of natural honey (Motallebnejad et al., 2008).

The literature review carried out previously included randomized or non-randomized studies that had sample groups of patients with head and neck cancer receiving RT and/or chemotherapy. In the present study; however, randomized controlled studies were included that were conducted with patients with head and neck cancer receiving RT treatment. In all the studies reviewed, it was found that honey was compared to different solutions (saline %0.9, lignocaine, benzydamine hydrochloride).

It was concluded that honey has positive outcomes in the prevention and severity of OM, but OM incidence was found to vary among studies. In all the studies reviewed, honey applied groups were found to have lower OM severity. In the study conducted by Khanal et al (2010), intolerable (grade 3 or 4) OM developed in 5% of the application group patients while in 75% of the control group patients (Khanal et al., 2010). Biswal et al (2003) found this ratio as 20% and 75% for application and control groups respectively.(Biswal et al., 2003) The study carried out by Alvi et al (2013) showed that only 13% of the application group developed grade 3 OM whereas grade 3 or 4 OM occurred in 40% of the control group (Alvi et al., 2013). In the study by Charalambous et al.(2018), on the other hand, while OM development was 22.2% in the application group, it fell to 2.8% in the seventh week. However, it increased from 30.6% to 44.4% in the control group (Charalambous et al., 2018). Other studies have reported OM development incidences in varying ways. In the meta-analysis and review studies previously conducted concerning the question, it was found that the

honey application groups had lower incidences of OM development than control group (Cho et al., 2015; Co et al., 2016; Münstedt et al., 2019). OM incidence and severity may vary by the treatment protocol (the medication given, its dose, route, frequency), type of disease and individual tolerance. In pediatric oncology patients, C-level evidence was revealed showing that honey was a preventive and treating method for chemotherapy induced OM (Friend et al., 2018).

In one study, pain accompanying OM was evaluated and honey application was found to reduce pain (Khanal et al., 2010). In patients receiving head-neck RT parotid gland function disorder may lead to acute or chronic xerostomia. Over time, this is followed by loss of taste, difficulty swallowing, eating, drinking, mouth-throat pain and resulting weight loss (Cady and Jackowski, 2014). In another study, patients were found to have swallowing, eating, drinking, mouth-throat pain and these complaints were found to be fewer in the honey applied group (Charalambous et al., 2018; Khanal et al., 2010). As a side effect of both cancer and cancer treatment, anorexia (loss of appetite) is seen among patients which is associated with inflammatory mouth causing difficulty chewing or swallowing, nausea, vomiting, anxiety or depression and leads to serious weight loss (Cady and Jackowski, 2014). In four out of the seven studies reviewed, weight loss was evaluated in patients and all the studies reported that patients in honey application groups had better weight maintenance (Alvi et al., 2013; Biswal et al., 2003; Charalambous et al., 2018; Motallebnejad et al., 2008). This can be explained with the fact that eating, drinking and swallowing get easier with decreased pain, which in turn provides better maintenance of weight. In this respect, it could be asserted that honey is effective in the prevention of OM and related secondary complications.

As mentioned above, OM causes mouth-throat pain, difficulty feeding and swallowing, which affects patients' quality of life negatively (Batlle et al., 2014; Carulli et al., 2013; Wang et al., 2015). It was seen that patients' quality of life was evaluated only in the study conducted by Charalambous et al (2018) which reported significantly higher quality of life for honey applied patients (Charalambous et al., 2018). This finding can be explained with the fact that honey applied patients have less trouble swallowing.

In the literature review, no study was found to report any complications regarding the use of honey and honey was found to be superior to other products in all variables evaluated.

Limitation

The present review has some limitations. Due to the fact that the number of studies concerning the effect of honey on the prevention of OM in patients with head and neck cancer receiving RT is limited and

that different implementations and solutions were used on control groups in these studies, the results cannot be generalized. Another limitation is the differences in the RT treatment protocols among studies. Moreover, differences in the evaluation instruments used in OM diagnosis may affect the results.

Conclusion

The present study reveals that when used regularly during RT, honey may have positive effects on such variables as OM incidence and severity, weight loss, pain and quality of life. Since honey is a cost-efficient method with no side effects, it is recommended that clinical studies should be continued. In order to prevent the misuse of honey implementation, which is a TAT method, by patients, there is a need for more evidence-based studies. It is recommended that randomized controlled studies be conducted with homogenous sample groups in order to determine the efficiency of honey on OM incidence and severity accurately.

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