New Horizons in Health Sciences

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ESSENTIAL OILS IN ALZHEIMER'S DISEASE TREATMENT

Emine Eda KAHRAMANOĞULLARI[1]

Arash Alizadeh YEGANİ[2]

INTRODUCTION

The increasing prevalence of Alzheimer disease in recent years has attracted significant research attention for the disease treatment and prevention. Acetylcholinesterase inhibition is the main approach for the disease treatment as mentioned. For this reason, the potential anti-acetylcholinesterase activity of some essential oils (EOs) from aromatic plants drew research attention for Alzheimer's disease treatment in recent years.

Alzheimer's disease

Symptoms

Alzheimer's disease (AD) is a neurodegenerative, chronic and progressive disease mainly characterised by the loss of cholinergic function and three categories of symptoms. The first category is called cognitive dysfunction, which comprises memory loss, reduced intellectual ability and language difficulties. The second category includes behavioural and psychiatric changes, such as agitation, depression and hallucinations (non-cognitive symptoms). The third category includes struggling to perform daily activities such as eating, shopping, driving and dressing. The symptoms of AD range from mild, such as memory loss, to severe, such as dementia. AD starts slowly and

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accumulates gradually over time; it is the prevalent cause of dementia (Burns and Iliffe, 2009).

Epidemiology

It is estimated that dementia affected 46.8 million people worldwide in 2015, and this figure is expected to double every twenty years (to 74.7 million and 131.5 million for the years 2030 and 2050, respectively) as the population cohort of elderly people more at risk peaks (Prince et al., 2015).

Risk factors

Age is the fundamental risk factor for the AD, whose incidence increases after 65 years of age (Querfurth and LaFerla, 2010). According to epidemiological studies, besides ageing, other factors leading to the reduced brain reserve capacity include low educational acquirement and mental training in early life; insufficient physical and mental activity in later life; and reduced brain size. Reduced brain reserve capacity causes some pathological changes associated with AD such as plaque or tangle formation in the brain. Although it has been found that head injury might be a risk factor for the disease, such mechanisms have not been clearly established. Moreover, vascular diseases such as hypertension, atherosclerosis, hypercholesterolemia, coronary heart disease, obesity, smoking and diabetes could be other risk factors, however it is unclear whether these initiate pathological cascade. Environmental factors may increase the risk, but genetic factors have a significant role on the development of the disease according to some studies (Blennow, de Leon and Zetterberg, 2006). Dietary influences have been suggested to reduce the risk of AD, such as antioxidants or unsaturated fatty acids, but the data are insufficient to support general recommendations (Blennow, de Leon and Zetterberg, 2006).

Pathological features

Aggregation of misfolded proteins over time in the aging brain causes inflammatory and oxidative damages, which lead to synaptic dysfunction and energy failure. Senile plaques called β-Amyloid peptide (Aβ) in the grey matter of the brain and neurofibrillary tangles (Figure 1), the hyperphosphorylated form of tau protein, are the distinguishing markers of the disease. Synaptic failure is also one of the main characteristics of the disease. Free radicals from dysfunctional mitochondria of the aging brain, ischemic disease, white-matter lesions and strokes considerably contribute to oxidative stress and cognitive decline. Inflammation also plays a significant role in the process of the disease (Querfurth and LaFerla, 2010).

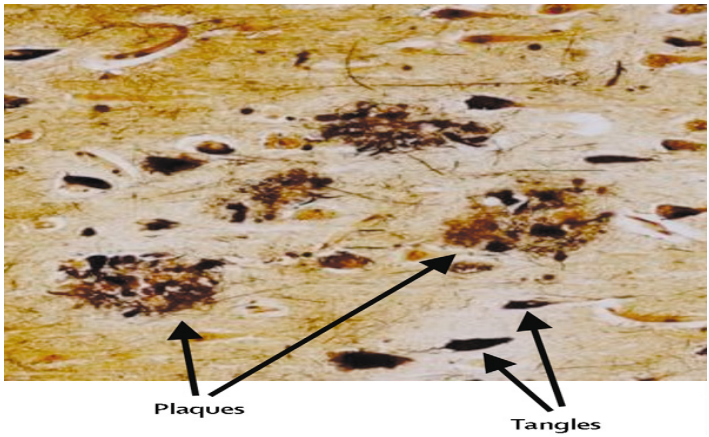

Figure 1: *"Cerebral cortex plaques and tangles with Alzheimer's disease"*

(Blennow, de Leon and Zetterberg, 2006, p.388)

Therapeutic approaches

- ***NMDA-receptor antagonist***

Over-activated NMDA receptors in AD are considered to trigger intracellular Ca2+ increase, leading to glutamate-mediated neurotoxicity. Therefore, NMDA-receptor

antagonists might prevent neurons from neurodegeneration and provide therapeutic potential for the treatment of AD (Klafki et al., 2006).

- ***Targeting Tau***

Inhibition of tau protein aggregation, activation of phosphatases and inhibition of tau kinases might be considered as a strategy for AD treatment (Klafki et al., 2006).

- ***Acetylcholinesterase inhibitors***

Acetylcholine is a neurotransmitter in the cholinergic system with muscarinic and nicotinic receptors in the peripheral and central nervous systems. Acetylcholinesterase is an enzyme which hydrolyses the cationic neurotransmitter acetylcholine into acetic acid and choline. The active site of the enzyme where acetylcholine hydrolysis occurs has a position at the bottom of the 20 Å deep gorge, including esteratic and anionic subsites. The peripheral anionic site is located at the neck of acetylcholinesterase, which is known to interact with amyloid β peptide, causing the formation of amyloid plaques and cholinergic neuron deterioration (Pohanka, 2011).

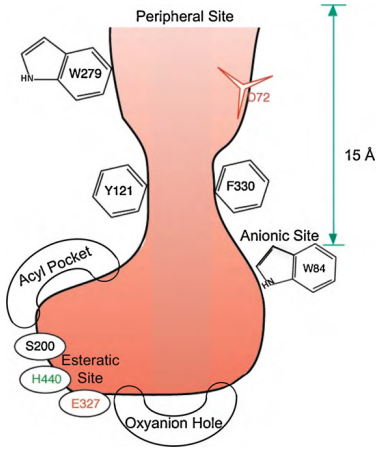

Figure 2: "Schematic view of the active-site gorge of TcAChE

The bottom of the gorge is characterized by several subsites: the 'anionic' site, with which the choline moiety of ACh interacts; the 'esteratic' site, which contains the three residues of the catalytic triad; the 'oxyanion' hole, and the acyl pocket, which confers substrate specificity. The PAS is located 15 Å above the active site, close to the mouth of the gorge" (Dvir et al., 2010, p.14).

Acetylcholinesterase inhibitors are mainly used to treat the symptoms of AD via elevating the acetylcholine level in the brain. Some currently available AChE inhibitors are tacrine and donepezil, which are synthetic, and the first approved drugs by US-FDA for the disease treatment; rivastigmine, which is derived from the natural alkaloid physostigmine; galanthamine, a natural 22 alkaloid from *Galanthus* spp., and huperzine A from *Huperzia serrata*. In recent years, the majority of discovered AChE inhibitors from natural sources have been from the alkaloid class, including isoquinoline, indole, piperidine, steroidal and quinolizidine alkaloids. On the other hand, non-alkaloidal AChE inhibitors such as some terpenoids, phenolic compounds and flavonoids provide promising results, supported by an increasing number of studies every year (Murray et al., 2013).

- ***Other therapeutic approaches***

Chronic intake of anti-inflammatory drugs, antioxidants, hormone therapy and mitochondrial protectors may slow down the disease progress. However, no convincing treatment has thus far been provided with those approaches for the treatment of AD (Huang and Mucke, 2012).

Essential oils

The history of essential oil use

Aromatic plants have been widely used for their medicinal and preservative purposes for thousands of years. The essential oils (EOs) formed by aromatic plants as secondary metabolites are mostly responsible for those effects(Edris, 2007). EOs, also called volatile oils, have been extensively used for virucidal, bactericidal, insecticidal, medicinal and cosmetic properties (including in massage therapy) since the beginning of civilization; the ancient Egyptians cultivated and produced aromatic oils for their spiritual, mental and physical healing properties in addition to their pleasant odour (Bakkali et al.,2008). The modern therapeutic use of EOs in aromatherapy is dated to Germany in the 16th century, and it was also used for the treatment of injured soldiers during the World Wars (Perry and Perry, 2006). Nowadays, approximately 300 commercially valuable EOs have an important place in pharmaceutical, cosmetic, sanitary, dentistry, agricultural and food industries(Bakkali et al., 2008).

Phytochemical properties

EOs are natural and complex substances with several components, mainly terpene hydrocarbons, which are formed by isoprene (CH2=C(CH3)-CH=CH2) units, in addition to esters, oxides, lactones, alcohols, phenol derived aromatic components, aldehydes and ketons (Bakkali et al., 2008).

Many EOs are formed by monoterpenes (formed by two isoprene units) and sesquiterpenes (formed by three isoprene units) whose biosynthesis are through mevalonate or non-mevalonate pathway. IPP (isopentenyl pyrophosphate) and DMAPP (dimethylallyl diphosphate) are the most important components of these pathways leading to isoprene unit formation (Chamorro et al., 2012).

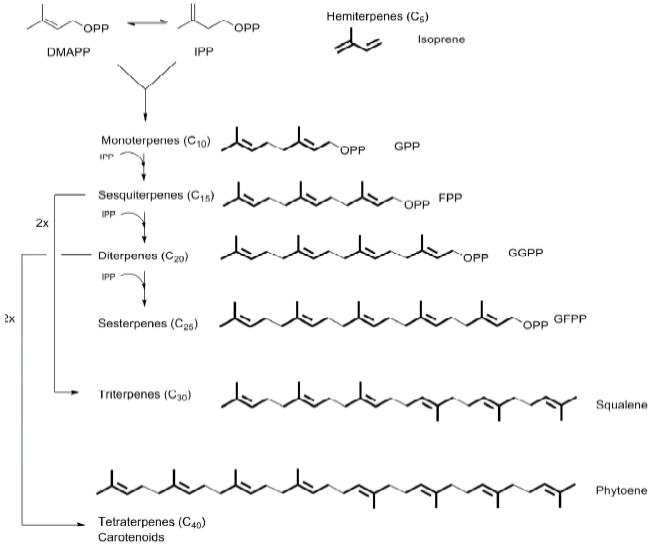

Figure 3*:" Overview of the different terpenoid skeletons generated by head to tail addition of isoprene units. IPP: isopentenyl diphosphate. DMAPP: dimethylallyl diphosphate. GPP:geranyl diphosphate. FPP: farnesyl diphosphate. GGPP: geranylgeranyl diphosphate.GFPP: geranylfarnesyl diphosphate." (Schwab & Wüst 2015, p.10592).*

Characteristics

Due to presence of those functional groups and olefenic double bonds, they are easily oxidizable by air, light and heat. They are volatile compounds that vaporize when exposed to heat, and they are lipophilic, soluble in non-polar solvents, alcohols, oils and waxes. Most EOs have lower density than water and they are colourless or pale

yellow in colour, with a characteristic odour (Djilani and Dicko, 2012). EOs from aromatic plants are not primary metabolites necessary for the growth and development of the plant; rather they are secondary metabolites with an important role in plant protection due to antibacterial, insecticide and antiviral qualities, as well as repelling or attracting herbivores and pollinating animals for pollen and seed distribution (Bakkali et al., 2008).

The isolation and structure elucidation

EOs can be isolated from many parts of plants, including the root, leaf, bark, wood, stems, twigs, fruits, flower and bud using different means of extraction methods such as steam or water distillation, which was first developed by Arab chemists and perfumers in the Middle Ages (Bakkali et al., 2008), supercritical fluid extraction, solvent extraction and expression under pressure (Edris, 2007). Those methods can be chosen according to the purpose of EO use.The chemical composition of the EO products can change according to the extraction method chosen if it affects the stereochemical types of molecules in the EO (Bakkali et al., 2008). Many aromatic plants are grown in temperate to moderately hot places like tropical or Mediterranean countries. Location, soil composition, climate, plant age, plant organ and vegetative cycle stage also affect composition, quality and quantity of EO. Therefore, consistent conditions are necessary to obtain uniform EO content. Gas chromatography coupled with mass spectrometry is a great tool for the determination and quantification of EO components and ensuring the favourable quality of EOs due to its efficiency, rapidity and simplicity (Bakkali et al., 2008).

The route of administration

EO can be taken into the body in three different ways: absorption through inhalation; transdermally via lotions

and massage etc.; or through ingestion in the form of capsules, medical preparations or food additives (Perry and Perry, 2006).

Safety

There is insufficient scientific evidence about the safety of EOs for human use, especially for pregnant women and children. However, some available scientific evidence suggests that bergamot, lemongrass, ylang-ylang EOs may cause serious health risks such as phototoxicity, teratogenicity and skin sensitization, respectively, but limiting the concentration of those oils may prevent such hazards. The most commonly encountered adverse reaction with EOs is allergic contact dermatitis, which is often caused by tea tree, cinnamon bark and laurel leaf EOs even in diluted concentrations (Tisserand and Young, 2013).

Biological activities

In accordance with the literature, the EOs and a broad range of their constituents possess many biological activities with noticeable therapeutic potential, including antiviral, antifungal and antimicrobial properties within a broad spectrum that can be used as antioxidant and antidiabetic agents, and in the treatment of cardiovascular disease (Djilani and Dicko, 2012). In recent times, it has been revealed that EOs from some plants may have a potential for the treatment of Alzheimer's disease due to acetylcholinesterase inhibitory activity, which is one of the most important approaches in disease treatment.

Relationship between essential oils and Alzheimer's disease

The acetylcholinesterase inhibitory properties of EOs have attracted the attention of researchers for the treatment

of AD in recent years. Many studies have been conducted in relation to AD among other psychiatric disorders. AD generally causes dementia by accumulating over time, which is an increasingly important public health issue given the imminent exponential increase in the number of people with the condition in the coming decades, as explained previously (Prince et al., 2015).

Some clinical trials investigating the relationship between the behavioural changes associated with the disease and EOs in aromatherapy showed some convincing evidence about healing properties of EOs on AD. For example, lavender (*Lavandula angustifolia* Mill.), lemon balm (*Melissa officinalis* L.), sage (*Salvia* species, especially *Salvia lavandulifolia* Vahl) EOs, applied independently or in combination, showed reductions in the symptoms such as social and behavioural withdrawal, insomnia, agitation and wandering. *Salvia* species especially seem to be promising due to its acetylcholinesterase inhibitory, estrogenic and anti-inflammatory properties (Perry and Perry, 2006).

Origanum species, especially *Origanum ehrenbergii* Boiss., *Origanum majorana* L., *Origanum syriacum* L. (Loizzo et al., 2009); *Pinus* species such as *Pinus heldreichii* subsp. *Leucodermis*, *Pinus nigra* J. F. Arnold, *Pinus nigra* subsp. *calabrica* (Loudon) A. E. Murray and *Citrus aurantiifolia* (Christm.)*Swingle, Citrus medica* L. cv. diamante from *Citrus* species are some good examples for AChE inhibition (Murray et al., 2013). There are also scientific data showing AChE inhibition of some isolated single compounds from EOs in the literature (Figure 4). Therefore, EOs have attracted much attention as potential treatments for AD (Dohi, Terasaki and Makino, 2009).

Identified volatiles with known AChE inhibitory activity

Up to 21 volatiles (Figure 4) were identified as active for the AChE inhibition(AChE inhibition of the volatiles only expressed as IC50 were included) from the EO of aromatic plants according to the literature. Monocyclic monoterpenes were predominantly identified active volatiles for AChE inhibition. Bicyclic monoterpenes, monoterpene alcohol, bisabolene-type sesquiterpenes, cyclic monoterpene, monoterpene keton and phenylpropene were other types of terpenes comprising those 21 active volatiles. Some volatiles were analysed for AChE inhibition by different researchers and different results were found. Camphor, α-pinene, β-pinene, 1,8-cineole can be given as the examples of this situation. Only one most relevant result from the same volatile was included in this paper.

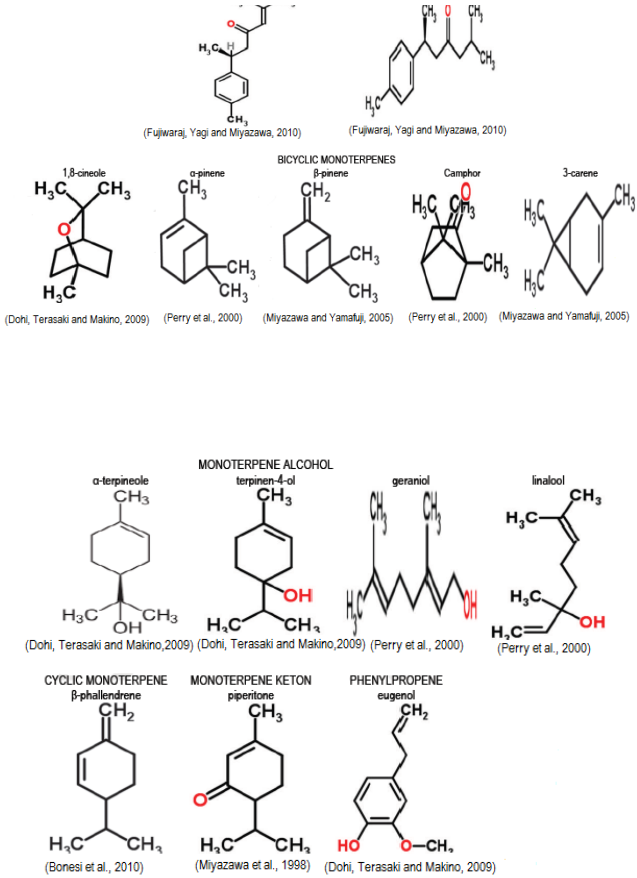

Figure 4: *Active volatiles previously were identified as having activity against AChE in the literature*

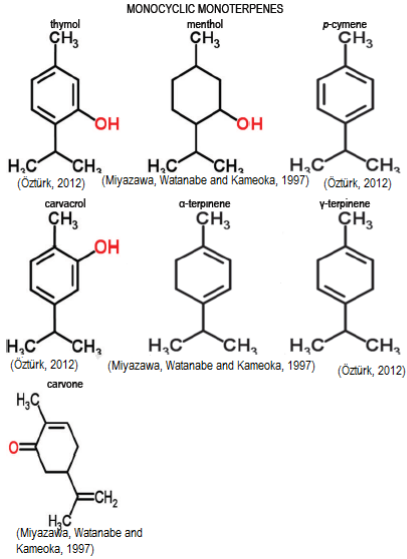

Figure 4 *cont.*

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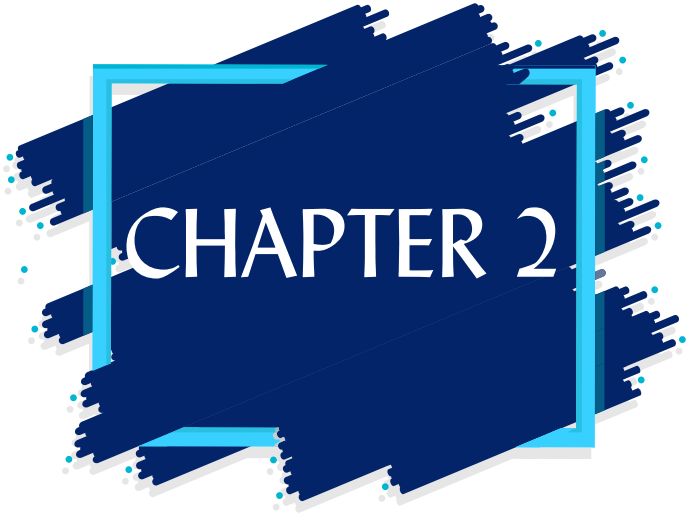
NURSING CARE PLAN IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING THE ROPER-LOGAN-TIERNEY FRAMEWORK

Bahar ÇİFTÇİ



NURSING CARE PLAN IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING THE ROPER-LOGAN-TIERNEY FRAMEWORK

Bahar ÇİFTÇİ

BACKGRAUND

Chronic obstructive pulmonary disease (COPD) is a progressive, irreversible permanent illness which interferes with normal breathing. (Elsherif and Noble 2011). Also, COPD is a slow progressive disease characterized by obstruction of airways and impaired airflow. In the World Health Organization report, among the causes of death in the world, it is stated that COPD which ranks fifth in 2001 will be in third place in 2020 (Tatlıcıoğlu 2007). COPD is an important cause of morbidity and mortality in the world. According to the Ministry of Health, COPD is the 11th most common cause of death in our country. (Burney et. al 2014)

At the end of the pathophysiological changes occurring in COPD, respiratory activity changes considerably, and dyspnea, fatigue and insomnia cause serious limitations while performing daily life activities (Duncan 20106). Functional losses affect the patient physically as well as psychologically, socially and economically (Smeltzer and Bare 2006). With the progression of the disease process, the increase in addiction and the restriction of social activities cause the patients to have difficulty in fulfilling the expected roles in the family and society, and cause anxiety, depression and social support needs. On the one hand, this process leads to an increase in the social support needs of patients while on the other hand they cause them to move away from social support resources. (Wall 2007, McCarthy et al. 2015)

The Roper-Logan-Tierney activities of daily living framework in conjunction with the nursing process model are valid tools in the management of the exacerbation of COPD. (Roper et. al 2000, Schober and Ash, 2006, Barnett 2007, Carpenito 2012, Birol 2018). To maintain confidentiality, an alias name will be used (Nursing and Midwifery Council, 2008), with the patient being referred to as M.K.

Nursing Story

The patient was a 58-year-old man. He is married and has two daughters and a son. M.K. is 68kg and 1.74cm. Her mother is hypertensive. There is no discomfort in the father. He is a university graduate and a retired teacher. M.K has been since 12-year-old patient with COPD. He had smoked since 18 years of age (28 years, 1.5 times a day) but when he learned that he had COPD 12 years ago, he stopped smoking with the help of his wife and physician. The patient, who regularly used drugs and went to the physician's controls, had complaints of respiratory distress, cough, mucus, bruising and chest pain 5 days ago. To pass these symptoms, the patient increased the dose of the drugs he used. However, he was admitted to the hospital because his complaints continued. COPD-fighting was hospitalized for treatment and follow-up. There is also hypertension for 5 years. Life Findings, Blood Pressure: 140 / 90mm / Hg, Heart Rate: 7min, Body temperature: 36.7 0C and Respiratory: 27min.

Table 1. *Laboratory Findings*

Results	**Reference Range**	**Results**	**Reference Range**
Hb: 13.7g/dl	**13.6-17.2**	**Glukoz: 681 mg/dl**	**75-100**
Hct: 41.6	**39.5-50.3**	AST:33U/L	**1-35**
WBC: 9mm^3	**4.3-10.3**	ALT: 27 U/L	**1-35**
PLT: 159mm^3	**150-450**	LDL: 145 U/L	130-230
BUN: 21 mg/dl	**6-22**	**Albumin: 2.9 g/dl**	**3.8-4.5**
Creatinin: 1.63 mg/dl	**0.51-1.95**	INR: 2.82	**2-3**
Na: 135 mEg/L	**135-145**	PTT: 25.5	**20-40**
K: 4.79 mEg/L	**3.5-4.5**	PT:19.49	5-20

Blood Gas Value

SaO2 %77.5, PaCO2109.5mmHg, PH7.33, HCO3 21.4 mmol/L, HCO3 21.4 mmol/L

Pulmonary function tests (PFTs) Value

COPD Phase=2nd Phase, **FEV1ml**=2920, **FEV1%**=85, **FVC%**=98, **FEV1/FVC**=59.5, **FEF25-75**=2180, **FEF27- 75 %**=57

Treatment: Avelox tb 1×1 08 PO Delix tb. 2×1 08 20 PO Pontpas flk 1×1 08 IV Lasix amp 1×1 08 IV Clexane 0.6 ml 1×1 08 SC Atrovent inh 4×1 08 14 20 02 Duphalac susp. 2×1 08 20 PO

The Roper-Logan-Tierney activities of daily living

1. Maintaining a Safe Environment Activity

There is a risk of infection due to the patient's age, ineffective airway clearance, lack of knowledge of the symptoms of infection and a decrease in pulmonary function. In addition, this is a major risk factor for our patient because hospitalization is always a source of infection for patients. In addition, our patient has invasive procedures. M.K expresses that the treatment regimen is complex and sometimes it is difficult to respond to the excessive requests (related to the treatment process) to the individual / family. In addition, because the individual is a chronic disease, long-term drug and oxygen means that it is difficult to use to use the tool.

2. Communication Activity

M.K uses prosthetic teeth. However, this situation does not impede the communication of the individual. The

patient has no problem with sensory organs. The individual said there was no limitation in communication.

3. Breathing Activity

M.K was admitted to the hospital with complaints of respiratory distress, cough, mucus, bruising and chest pain. The patient is currently experiencing increased dyspnea. There is also a cough and mucus complaint in the individual.

4. Eating and Drinking Activity

The patient is taking a salt-free diet because he has hypertension. It fits the individual diet in the hospital environment and home. The patient is 68kg. No food that he doesn't like. He said he could eat some kind of food. However, M.K said that he had lost 2 kilograms due to her appetite reduction due to difficulty in breathing and fatigue. Independent in patient nutrition. Oxygen has dryness on the lips for taking. No difficulty swallowing.

5. Elimination Activity

M.K can perform the discharge requirement independently. The individual who meets the need for defecation every day while in his home, said that he did not resolve the need for emptying for 4-5 days. He said he had pain in his abdomen and difficulty during excretion. Distention of the individual is available.

6. Washing and Dressing Activity

M.K is half-dependent in this activity due to dyspnea. His wife helps her husband with personal hygiene. The pajamas of the individual are clean. His wife, without the personal care of breathing difficulties and was unable to do so, she said. The bed is clean and tidy.

7. Controlling Temperature Activity

The body temperature is 36.7 ^{0}C. Individual's clothing is suitable for the temperature of the environment.

8. Mobilisation Activity

Breath difficulty, ineffective breathing, cyanosis is present in M.K. Dyspnea is observed during movement. He's dependent on his wife when he moves.

9. Working and Playing Activity

M.K is a retired teacher. He spends his spare time reading books, worshiping, spending time with his grandchildren and watching television.

10. Expressing Sexuality Activity

M.K was acting according to age and gender. His speech style, tone of voice, clothing, and behavior were behaviors specific to his own kind.

11. Sleeping Activity

M.K had suffered dyspnea at night, so he often woke up at night and said he could not sleep. The individual said that he was comfortable with 3 pillows at night. It was observed that the person was making sweets during the day.

12. Death and Dying Activity

M.K meets the death naturally. No fear of death. Religious beliefs have a positive effect on coping with diseases.

Table 1. *Nursing Care Plan*

Daily Life Activities	Descriptive Features /Signs and Symptoms	Etiology and Nursing Diagnosis	Purpose/ Expected Patient Results	Nursing Care	Evaluation
Maintaining a Safe Environment Activity	---------- ----------	Depending on the age of the individual (58), ineffective airway cleaning, decrease in pulmonary function, presence in the hospital environment and invasive interventions: **RISK of INFECTION**	To know the risk factors related to infection and to take appropriate measures to protect against infections, No nosocomial infection during hospital stay	**Evaluation** The patient was evaluated for risk factors such as IV interventions. Such attempts may break the patient's defense mechanism. The patient's white blood cells (WBC) were observed. **(WBC: 9mm^3)** Rising WBC indicates that the body's pathogens are fighting microorganisms. Symptoms of infection were observed. (**Body temperature: 36.7 ^{0}C)** Nutritional status was evaluated by examining the patient's weight and weight loss history. **1 kg loss in 1 week.** Malnutrition patients may have poor cellular immune response to pathogens and therefore may be more susceptible to infection. **Therapeutic intervention** Appropriate aseptic technique was applied in invasive procedures and these procedures were taught to the patients and relatives. Water, soap and brushing are the most effective ways to remove microorganisms from hands. Therefore, hands were washed when contacted with each patient. Visitors may be restricted if it is thought that they will not cause psycho-social harm. The visitor and staff are prevented from entering the patient's room without handwashing. As it was not contraindicated, 3000 ml of fluid intake per day was encouraged. The importance of changing the water used to moisten the oxygen was mentioned. Because lung and bronchial secretions would increase movement, coughing exercises was frequently applied to the individual and encouraged to	No signs of infection were observed. (Body temperature: 36.7 ^{0}C WBC: 9mm3) The patient did not have nosocomial infection during his hospital stay.

				respiratory tract infections, including pneumonia, and may increase the severity of diseases such as COPD. The use of antibiotic drugs ordered by the physician **(Avelox tb 1 × 1 08 PO)** was regulated and taught to the individual. These substances provide a toxic effect against the pathogen or delay the growth of the pathogen. **Continuity of Care / Training** The patient and his relatives were instructed to wash hands frequently before, especially after meals, after self-care, after the need for toiletries. Hand washing is the easiest and most economical method of preventing the spread of infection. The importance of using antibiotics as prescribed was taught to the patient and his relatives.	
Communication Activity The patient has no problem with sensory organs. You can communicate with your surroundings comfortably.					
Breathing Activity	Abnormal breathing sounds (rustling, wheezing and rales) Changes in respiratory rate and depth Cough Hypoxemia / cyanosis Difficulty in breathing. Tachycardia Increase in	Depending on hyperplasia and hypertrophy of the mucous glands, increased secretory production in the bronchi, secretion intensity and bronchosp	Ensuring the openness of airways The individual expresses verbally that he breathes comfortably	**Evaluation** Airway patency is our priority, especially in cases of trauma, acute neurological disorder or cardiac arrest. Therefore, the airway was evaluated for clarity. For the presence of normal or abnormal breathing sounds, the lungs were rested with a stethoscope. Wheezing: It may be due to increased airway resistance. Roughing of lung sounds: May indicate the presence of mucus in large amounts of large respiratory tract. The patient's respiration was assessed; rate **(Rhythmic)** depth, number **(Respiratory: 27min)**, normal nostrils, shortness of breath **(increase present)**, appropriate position for respiration (breathing more easily in orthopnea position). Abnormalities indicate breathing difficulty. Vital signs and temperature changes were evaluated. **(Life Findings Blood Pressure: 140 / 90mm / Hg Heart Rate: 70 min, Body Temperature: 36.7 ^{0}C Respiratory: 27min).** Cough was evaluated for efficacy and efficiency. Possible causes for	Respiratory : 27min SaO_2 92%, $PaCO_2$ 72 mmHg reduced amount of mucus. It was observed that the patient learned deep breathing and cough exercises.

	mucus	asm: **FAİLURE to MAİNTAİN AİRWAY PATENCY**		ineffective cough include: respiratory muscle fatigue, severe bronchospasm, thick persistent secretions and others. Presence of mucus; color, quantity, odor. Infection, bronchitis, smoking may result. Mucus may be present in the symptom of infection. Arterial blood gases were evaluated. **(Blood Gas Value SaO_2 77.5%, $PaCO_2$ 109.5mmHg, PH7.33, HCO_3 21.4 mmol / L, HCO_3 21.4 mmol / L).** Increased PaCO2 and decreased PaO2 are among the findings of respiratory failure. The patient's knowledge about the disease process was evaluated. Patient education can vary depending on the patient's cognitive level, as well as an acute or chronic disease condition. **Therapeutic interventions** Cough increases efficiency of respiratuary and provides secretion of secretions. Therefore, the patient was assisted to perform cough and breathing exercises. Patient was trained for; correct sitting position, use of pillows when cough begins, use of abdominal muscles for stronger cough. In cooperation with the patient was made trained about the importance of frequent position change. These methods can help to prevent the formation of secretion and to help the lung enlargement to prevent atelectasis. The patient was taught the correct sitting technique so that the patient could easily remove the secretions. **(The patient's bedside was lifted 45 degrees and was also seated in the chair)** Because it is not contraindicate Oral intake of fluids was encouraged for prevent secretions from drying out, and facilitated secretion. Ordered drugs **(Avelox tb, Atrovent inh)** 8 were given according to the correct principle. Applications for postural drainage and percussion were performed at least 1 hour after eating. Postural drainage and percussion help to release secretion.	

				After eating, it prevents the risk of aspiration. **Continuity of Care / Training** Deep breathing and cough exercise techniques were taught to provide airway clearance in patient's home too. The patient was trained about the side effects of the drugs and indications. The patient was trained that there may be inaccuracies in the use of inhaled drugs. The patient was informed about the environmental factors that accelerated respiratory problems. The patient was trained about the harmful effects of smoking, including passive smoking.	
Eating and Drinking Activity	Losing 2 pounds in 3 days Rejection of food due to secretions Change in the sense of taste due to secretions **Albumin: 2.9 g / dl** **K: 4.79 mEg / L** Inadequate food intake Indifference to food	Depending on increased metabolic requirement due to respiratory difficulty, dyspnea and increased secretion, fatigue caused by decreased appetite: **LESS NUTRİTİON THAN**	Providing the daily nutrients to be arranged according to the metabolic needs and activity of the patient	**Evaluation** The actual weight of the individual **(Weight: 68kg Height: 1.74 BMI: 22.5)** was evaluated. The feeding history of the patient and her immediate family. **(Because he is a patient with hypertension, M.K has on a salt-free diet.)** Etiological factors that reduce nutrient intake **(respiratory distress and fatigue result)** were determined. Because many psychological, psychosocial and cultural factors may affect the type and amount of the food, the patient's attitudes towards food **(No food he dislikes. He expressed that he can eat kinds of food)** was discovered. The patient's food was observed. The patient's room was ventilated before the meals and bad odors were eliminated. Laboratory values showing the level of nutrition were monitored. Serum electrolyte values were checked. **(Albumin: 2.9 g / dlK: 4.79 mEg / L)** **Therapeutic interventions** The food preferences of the individual were evaluated and with the nutritionist was cooperated to provide nutritional support. Providing a pleasant environment, bringing the patient to the appropriate position and providing a good mouth and teeth hygiene methods were	He expressed his appetite increasing orally. But weight gain has not yet been achieved. **Albumin: 3.2 g / dl**

		BODY REQUİR EMENT		supplied. In cooperation with the relatives of the patients, the patients were informed about the food they would like to bring from the house. Individual was encouraged for exercise and information was given about eating fruit. **Continuity of Care / Training** Four basic food groups and certain minerals or vitamins were informed. The patient was advised to use a balanced diet. The importance of adequate caloric intake was explained. The choice of high calorie / protein foods for weight gain was encouraged.	
Eliminati on Activity	4-5 days of defecation Hard, dry gaita Pain in the abdomen Distention	Depending on inactivity due to activity intoleranc e, side effects of the drugs and disruption of the habit of defecation of the patient; **CONSTİ PATİON**	Patient will perform bowel excretion every 2-4 days Patient and patient relatives can prevent recurrence of constipatio n	**Evaluation** The habit of defecation of the individual **(not being able to defecate for 4-5 days)** was evaluated. It is important to determine what was "normal" for each individual. M.K said that he normally fulfilled the need for defecation every day before hospitalization. Previous eating habits, eating hours and fluid intake were assessed. Changes in eating time, food type, anxiety and stress can lead to constipation. The activity of the individual was determined. **(M.K., difficulty in breathing, ineffective respiration, cyanosis is present. Dyspnea is observed during movement. Dependent on his wife while moving.)** Long-term bed rest, lack of exercise and inactivity contribute to constipation. The current drug use of the individual was evaluated. Some types of drugs (iron and calcium supplements, antacids **(Pontpas)** and antihypertensives **(Delix tb., Lasix amp)** may cause constipation, and the patient also uses Duphalac suspension for constipation. Because many people were reported to be limiting the ability of the bowel movement to be away from home, it was evaluated whether there was an appropriate toilet for defecation. The patient said that he could use the hospital toilet comfortably. **Therapeutic interventions**	The patient's constipatio n was resolved. The patient had defecation every day. He was informed about the importance of the patient's fibrous food, movement, and adequate fluid

				Because it was not medically contraindicated, 3000 ml of 2000 daily fluid intake was encouraged per day. Fluid intake may promote intestinal excretion. Since fiber foods are essentially unchanged in the intestine, they are easy to digestion when they reach the colon. Therefore, feeding with fiber foods **(eg, raw fruits, fresh vegetables)** was encouraged. The patient was encouraged to consume freshly squeezed juice, cereals and dried fruits. These nutrients are natural "Cathartics" with high fiber content. The patient was encouraged to exercise physical activity and regular exercise as abdominal exercises strengthened abdominal muscles. But, since the patient had difficulty in breathing, ROM exercises were performed and taught. **Continuity of Care / Training** High-fiber diet may cause discomfort and swelling in the abdomen. Because a gradual increase in dietary fiber intake is recommended, cooperation with the dietitian was made. The importance of the following information was explained to the patients and their relatives. - A balanced diet with sufficient fiber, fresh fruit, vegetables and cereals - Adequate fluid intake (eight cups per day or 2000-3000 ml per day) - Regular meal - Successful intestinal training (Performing regular defecation every day at the same time) - Adequate and regular time allocation for defecation - Regular exercise / activity	intake.
Washing and Dressing Activity	To get help from his wife to ensure personal hygiene	Depending on cyanosis Energy shortage, respiratory	The patient performs the self-care activities	**Evaluation** Daily life activities **(eating-drinking, dressing, movement etc.)** ability was evaluated regularly. **(His wife is helping him with personal hygiene. The individual's pajamas are clean. when his wife is not next to him, he is having respiratory distress while he is doing his personal care and he cannot do it. His bed is clean and regular.)**	Because the patient's dyspnea continues, the

	Respiratory distress during self-care	distress, fatigue, exercise dyspnea; **INSUFFİCİENCY İN İNDİVİDUAL CARE**	safely.	Fatigue **(fatigue present in the patient)** was evaluated during dressing. Respiratory distress of the individual (half dependent due to dyspnea) was evaluated. Respiratory distress of the individual **(half dependent due to dyspnea)** was evaluated. **Therapeutic interventions** Her independence was encouraged, but when he was unable to perform dressing activity, he was asked to seek support from his wife. Sufficient time was provided for the patient to complete the tasks. Privacy was ensured during dressing. The patient rested before doing daily activities. The patient was informed about the use of non-zippered clothes in the patient's home as it would facilitate the patient's function and provide comfort. **Continuity of Care / Training** It was taught that the relatives of the patients should help them to promote the independence of the patient.	dressing activity is still half-dependent to his wife.
Controlling Temperature Activity The body temperature is 36.7 0C. Individual clothing is suitable for the temperature of the environment.					
Mobilisation Activity	**SaO_2: %77.5** **FEV1/FVC :59.5** Cyanosis Increase in Breathing Wheezing Fatigue Verbal expression of shortness	Depending on imbalance between ineffective breathing, fatigue, oxygen requirement and consumption;	To be able to move without pain, dyspnea and fatigue, To be able to express enough sleep and rest,	**Evaluation** Causes of fatigue and perception of the patient were determined. The mobility of the patient was evaluated. Fatigue and dyspnea were detected at the time of movement. As the necessary energy reserves were required for the activity, the patient's nutritional status **(2kg loss due to difficulty in breathing and fatigue)** was evaluated. Prior to the activity, the patient's cardiopulmonary status **(Vital signs: Blood Pressure: 140/90mm/Hg Pulse: 70min, Body temperature: 36.7 ^{0}C, Respiratory: 27min, Extracostatic hypotension, increased oxygen activity, dyspnea and wheezing, present weakness and fatigue)** evaluated. Since the activity intolerance affected the sleep patterns, the patient's sleep	The patient's activity intolerance was reduced but not completely eliminated. The patient can easily perform the

	of breath while walking	**ACTIVITY INTOLERANCE**	Showing that you tolerate increased activity	was evaluated patterns over the last few days **(he had suffered dyspnea when he woke up, for which reason he would frequently wake up at night and could not get any sleep. M.K said that he would be comfortable with 3 pillows at night sometimes).Therapeutic interventions** The patient was encouraged to ensure adequate resting, especially before meals and exercise. The material needed by the patient to reduce the energy expenditure was placed close to the patient. The patient was encouraged to do the exercises he could do with less energy. **Maintenance Continuity / Training** Excessive physical activity symptoms were taught to the patients and their relatives. The importance of continuity of physical activity at home was taught to prevent muscle weakness. Because provide longer-term activity and reduce oxygen consumption, energy saving techniques were taught. - Doing any work while you're sitting down. -Sightly change positions. - Rest for at least 1 hour after meals before starting a new activity. ROM exercises were taught to the patients and their relatives.	ROM exercises.
Working and Playing Activity M.K is a retired teacher.					
Expressing Sexuality Activity M.K was acting according to age and gender. His speech style, tone of voice, clothing, and behavior were behaviors specific to his own kind.					
Sleeping Activity	waking up at night often Not getting sleep Not enough	Depending on hypoxemia, mucus, side effects of	To state that the symptoms of insomnia are	**Evaluation** In a normal environment, the sleep pattern was evaluated **(it was comfortable to sleep for lack of respiratory distress before hospitalization).** Factors preventing sleep were identified. **Therapeutic intervention**	Because the patient's dyspnea is diminishing, he can

	rest Comfortable with 3 pillows at night Sleeping short during the day. Stretch	drugs and respiratory distress **SLEEP PATH DISORDERS**	reduced, To say that you have slept more and rested, To say enough energy to maintain your daily life activities	The patient was informed that he should stay away from any severe food, caffeine or smoking stimulants. Excessive fluid intake before bedtime was prevented. Daytime ROM exercises were increased as indicated. Exhausted activities were prevented from going to bed before bedtime, as excessive fatigue could cause insomnia. Because milk contains L - tryptophan, it facilitates sleep. A suitable environment was provided for the individual to sleep or to rest. **(the individual is comfortable with 3 pillows at night).** It was suggested that a relaxing activity be done before sleeping, such as a pleasant reading book, relaxation exercises, a warm bath, calm music. **Maintenance Continuity / Training** Factors preventing sleep were identified and the most appropriate methods to provide a solution were taught to the patient and to the patient. Non-pharmacological sleep development techniques were taught.	now sleep more comfortably.
Death and Dying Activity M.K meets the death naturally. No fear of death. Religious beliefs have a positive effect on coping with diseases.					

CONCLUSION

In this study, the care requirements of M.K., who had COPD, were determined. The nursing care plan was prepared in line with Nursing process and Roper-Logan-Tierney Model of Living. A nursing care plan was prepared by considering individuality in life. Short and long term targets were determined and appropriate nursing interventions were made to achieve the targets. Because it is extremely important to educate patients and caregivers on disease, treatment and nutrition, finally, patient education was done in order to do the same applications in the patient's home.

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MELATONIN IN THE TREATMENT OF ORAL MICROBIAL DISEASES

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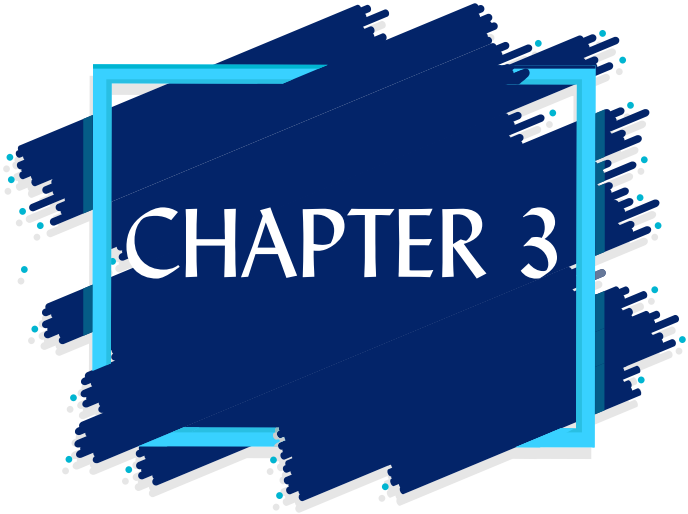

MELATONIN IN THE TREATMENT OF ORAL MICROBIAL DISEASES

Banu UYGUN CAN

Melatonin (MLT) (*N*-acetyl-5-methoxytryptamine) is a substance released by several organs, including the pineal gland, retina, bone marrow, the gastrointestinal tract and the immune system, and has the primary function of regulating the circadian rhythm (Siu, *et al.*, 2006; Cutando, *et al.*, 2011).

MLT is generally classified as a hormone. However, the molecule exhibits paracrine, autocrine and antioxidant effects with actions dependent on or independent from various receptors (Tan, *et al.*, 2003). Due to its highly lipophilic characteristics, MLT penetrates all cells in the organism. Salivary melatonin concentrations are 15 to 33% of plasma concentrations. Approximately 70% of plasma MLT binds to the albumin but it does not enter the saliva to a significant extent. Measurement of salivary MLT concentrations is a reliable technique to monitor the circadian rhythms of MLT (Laakso, *et al*., 1990; Hardeland, *et al*., 2006).

In healthy individuals, blood MLT levels peak at nighttime (4-8 hours after dark) and maintain the trough during the day (Simonneaux and Ribelayga, 2003). Nighttime melatonin levels are generally 10-20 times higher compared to daytime concentrations (Simonneaux and Ribelayga, 2003; Arendt, 2000; Czesnikiewicz-Guzik, *et al*., 2007; Reiter, 1991a). Melatonin production declines after the age of 40 to 45, and gradually drops with aging (Reiter, 1991b).

MLT has several physiological functions, including the control of circadian rhythms (Redman, *et al*., 1983; McArthur, *et al*., 1997), regulation of body temperature

(Dollins, *et al*., 1994), and regulation of sexual development in different parts of the body (Esquifino, *et al*., 1987; Kennaway and Rowe, 1995). It is also involved in activation of the immune system (García-Mauriño, *et al*.,2000; Guerrero, *et al*., 2002). In the oral cavity, MLT is recognized as an important substance with paracrine effects on nearby cells (Tresguerres, *et al*., 2002). Also, it exhibits antioxidant and antiinflammatory function and plays a major role in bone formation and reduction of bone resorption (Rodriguez, *et al*., 2004; Reiter, *et al*., 2016; Cutando, *et al*., 2008; Lian, *et al*., 2016; Clafshenkel, *et al*., 2012).

Although there are studies on the role of MLT in tooth development (Kumasaka, *et al*., 2010), further research is needed. MLT suppresses the tissue damage caused by medicines with toxicity due to the formation of free radicals (Reiter, *et al*., 2002). MLT has also been successfully used after oral surgery for its antioxidant, stimulant and protective effects on intracellular enzymes involved in the repair process (Cutando, *et al*., 2007).

MLT is excreted into the oral cavity by saliva and can potentially have oral health benefits not yet determined. Passing from blood to saliva, MLT can play a major role in the suppression of oral diseases. In addition, it can have beneficial effects on periodontal diseases, herpes and mouth cancer (Cutando, *et al*., 2011). As a result of pathologies characterized by the dysfunction of salivary glands, individuals can have high capacity to develop oral cavity diseases. Local or systemic administration of MLT can protect the oral cavity against various inflammatory and infectious processes in these patients. The functional aspects of MLT in the oral cavity requires further studies and can constitute a productive field of research.

The aim of this review is to critically analyze, summarize and emphasize the studies on the significance of MLT in the treatment of oral microbial diseases.

Methods

Scientific databases PubMed, ISI and Science Direct were extensively scanned for all of the related literature.

Keywords used for the scan:

- melatonin
- melatonin and the oral cavity
- melatonin and cancer
- melatonin and microorganisms, bacteria, virus, fungus

The results were evaluated carefully and key findings on the use and effects of melatonin on oral cavity diseases are summarized below.

The review is divided into the following sections:

1. Melatonin and periodontal diseases;
2. The effects of melatonin on oral cancers;
3. Melatonin as an antimicrobial agent;
4. Melatonin and tooth cavities;
5. The other effects of melatonin on the oral cavity;
6. Melatonin and herpes viral infection;
7. Melatonin and candidiasis;
8. Conclusion

1. Melatonin and periodontal diseases

Periodontal disease is an inflammatory condition characterized by gingival bleeding, periodontal pocket formation and destruction of connective tissue. The disease begins in dental biofilm with stimulation of the immune system against microorganisms. The most common form of periodontal disease in humans is gingivitis caused by plaque, and can progress to more aggressive forms of periodontitis. Advanced forms of the disease involve severe loss of gingival tissue and alveolar bone.

An important aspect of periodontal disease is the formation of free radicals, some originating from oral bacteria and others from inflammation and induction of immune response (Gustafsson and Asman, 1996; Battino, *et al*., 1999). Activation of proinflammatory molecules causes destruction of periodontal tissue (Kimura, *et al*., 1993). This increase in free radicals is accompanied by a decrease in antioxidant defense. This imbalance can potentially cause severe deterioration in periodontal tissues (Sies, 1997). MLT plays an important role in the control of this disease with its antioxidant and free radical scavenging properties.

Potential therapeutic effects of MLT on periodontitis have been documented in *in vitro* animal studies as well as clinical studies (Najeeb, *et al*., 2016).

The association between the periodontal conditions and salivary MLT levels is still inadequate (Srinath, *et al*., 2010). Cutando *et al.* (2006) in a study on the relationship between salivary MLT rates and periodontal disease stages found an inverse correlation: salivary MLT levels decline as the severity of periodontal disease increases, which indicates that MLT can offer protection against bacterial infections.

In another study, mean levels of MLT in the salivary and gingival crevicular fluid in four groups in different stages of periodontal disease were compared, and a statistically significant difference was found between healthy patients and patients with chronic or aggressive periodontitis. This study also reported comparable levels of MLT in salivary and gingival crevicular fluid, confirming the results obtained in previous studies (Almughrabi, *et al.,* 2013). In a similar study conducted by Gómez-Moreno *et al.* (2007), it was reported that cases of periodontal disease had significantly lower plasma and salivary MLT levels compared to the healthy control group.

Some studies corroborate the idea that MLT can be utilized as a biomarker to monitor the severity of periodontal disease and present a potential treatment strategy (Ghallab, *et al.,* 2016; Lodhi, *et al.,* 2016).

Due to the antioxidant and antiinflammatory effects of MLT, an increase in salivary MLT levels can promote the defensive reaction of the organism to the periodontal inflammatory process. Several studies revealed both salivary (Srinath, *et al.,* 2010; Cutando, *et al.,* 2006) and gingival crevicular fluid (GCF) (Srinath, *et al.,* 2010) MLT levels, which suggest that MLT can have a protective role against periodontal disease. Salivary and gingival crevicular fluid levels declined as the stage of periodontal disease increased, which indicates that MLT protects the body from external bacterial aggression (Srinath, *et al.,* 2010; Cutando, *et al.,* 2006).

A certain extent of antimicrobial effects, activation of the immune system and the antiinflammatory and free radical scavenging effects can partially account for the protective role of MLT on periodontal tissues (Poon, *et al.,* 1994; Reiter, *et al.,* 2000).

In addition to its multifaceted actions, another advantage of MLT is that it can be readily combined with other medicines for its relative safety and low rate of adverse events. Several aspects of the possible therapeutic contributions of MLT and its antagonists are still discovered, and both pivotal studies and clinical studies on the subject would inspire curiosity.

2. The effects of melatonin on oral cancers

MLT prevents the damage inflicted on healthy tissues by radiotherapy routinely used to treat oral cancers (Reiter and Meltz, 1995). A recent *in vitro* study showed that MLT can prevent metastasis of oral cancer by inhibiting the activation of metalloproteinase-9 (Yeh, *et al.,* 2016). Therefore, MLT-containing oral rinses, gels and toothpastes can be useful in the prevention of mouth cancer (Najeeb, *et al.,* 2016).

MLT is a circadian signal that mediates the variations of seasonal reproductive cycles in photoperiodic mammals and affects various aspects of the circadian rhythm by binding to membrane receptors (Blask, , *et al.,* 2005).

More recent studies showed that functions of MLT are much more complex than only those on circadian and circannual cycles, indicating that there is a relationship between the aspects of intercellular functions and MLT containing mechanisms independent from the effects on receptors. MLT is only one of the many factors that can control cell proliferation. In this group, MLT is the only known chronobiotic and hormonal regulator of neoplastic cell growth. MLT is cytostatic and inhibits cancer cell proliferation at physiological circulation concentrations (Mirick and Scott, 2008). Several *in vitro* studies reported oncostatic actions causing reduction in malignant cell growth and/or tumors in breasts, prostate

or other tumors (Cos, *et al.,* 2002). Production and release of almost all hormones follows an approximately 24-hour cycle. Lifestyle factors (e.g. working night shift or sleep disorders) can disrupt the circadian rhythm, change endocrine function and interrupt the regulation of reproductive hormones potentially implicated in the etiology. For example, effects of hormone-related diseases like breast or prostate cancer (Czeisler and Klerman,1999; de Almeida-Chuffa, *et al.,* 2019). Therefore, visually impaired individuals, for instance, do not suffer the prevention of MLT production that affects night workers. Breast tumors are observed less frequently among blind women (Flynn-Evans, *et al.,*2009). In 2007, IARC (WHO) supported this by classifying it as "shift-work that involves circadian disruption." The hypothesis is based on the following: MLT is a hormone produced at night under the control of the circadian clock and light can suppress MLT synthesis. As an indoleamine, MLT acts as an oxygen radical scavenger that can damage DNA, in which case its deficiency can cause cancer (Kantermann and Roenneberg, 2009).

Another mechanism that can account for such direct anticancer activity works as follows: MLT can interact with nuclear receptors and exhibit antimitotic activity with a direct effect on hormone-dependent proliferation. MLT can affect regulation of the cell cycle and promote the expression of p53, a tumor suppressor gene (Martín-Renedo, *et al.,*2008).

Therefore, although we are aware that there are different potential ways MLT can show anticancer action, we have limited knowledge in the context of the oral cavity. Very few studies have been identified on MLT and its anticancer activity in the oral cavity (Scully, *et al.,*2000).

High-risk human papillomaviruses (HPVs) are causative agents of cervical and many other anogenital malignancies and oral carcinoma (Tommasino, 2014). Although different types of HPV are regarded as cancer-associated agents, HPV-16 and HPV-18 are the most frequently seen genotypes (Giuliano, *et al.,* 2015; Markowitz, *et al.,*2016). Limitations of available prophylactic HPV vaccines emphasize that there is a growing need for new approaches in the eradication of HPV-associated cancers and development of therapeutic HPV vaccines for the treatment of HPV-associated lesions should remain a main objective (Karaki, *et al.,* 2016; Kawana, *et al.,*2009). Based on these safety and immunological profiles of MLT, it was observed that administration of MLT during DNA vaccination increased the ability of cancer vaccines to enhance CD8+ T cell stimulation to provide better protection against a TC-1 tumor. The data show that MLT can be beneficial as an adjuvant to DNA vaccines against HPV-associated cancer types (Baghban-Rahimi, *et al.,* 2018).

On the other hand, the same strains of *Veillonella, Streptococcus* and *Propionibacterium* were found among oral and atheroma plaque in the study of 454 pyrosequencing of oral, intestinal or atheroma plaque samples taken from 15 patients with atherosclerosis and 15 patients in the control group conducted to elucidate the relationship between oral and systemic diseases (Koren, *et al.,* 2011). Evidence is growing that oral microbiome is involved in the etiology of oral and gastrointestinal (stomach and pancreatic) cancers. If such a relationship is established, it will be possible to identify the risk of cancer noninvasively with oral bacteria profile, employ it as an additional indicator of known risk factors of cancer, and prevent cancer with microbial prophylaxis.

3. Melatonin as an antimicrobial agent

MLT has antimicrobial properties against various types of bacteria and viruses (Tekbas, *et al.,* 2008; Boga, *et al.,* 2012). On the other hand, no studies have been identified that test the effects of MLT against cariogenic bacteria like *S. mutans* and *Lactobacillus*. In a study conducted by Mechin and Toury (1976), it was reported that rats that received intraperitoneal MLT injection had a significantly lower number of cavities compared to animals that didn't receive MLT injections. It can be demonstrated that the direct antimicrobial effect of MLT synergistically supported with its immunomodulator and antioxidant properties is a strong weapon against a wide range of oral infections (Najeeb, *et al.,* 2016).

Candida constitute a common microbial flora in human oral cavity, gastrointestinal system and urogenital system. On the other hand, they can cause virulence and, in immunosuppressed patients or individuals undergoing prophylaxis or antimicrobial chemotherapy, they can cause superficial or deeply located infections (candidiasis). Severe cases of candidiasis can be fatal with morbidity and mortality rates up to 60% (Ghannoum and Rice, 1999). Conventional treatment of antifungal agents includes polyenes, azoles and echinocandins. However, these involve weak pharmacokinetics or serious side effects. Moreover, resistant strains frequently emerge in the clinical setting (Morschhäuser, 2010). Therefore, there is a desperate need for new antifungal agents.

The immunoregulatory effects of MLT on fungal infections were shown in a rat model of *Candida* sepsis (Yavuz, *et al.,* 2007) Another study showed that MLT reduces oxidative stress during candidiasis (Gomez-Moreno, *et al.,* 2010)

Biofilm formation is a primary virulent characteristic of *Candida* and fungal cells buried in the biofilm are less sensitive to antifungal agents (Ghannoum and Rice, 1999; Morschhäuser, 2010).

Strong anti-biofilm effects of MLT against *C. parapsilosis* suggest that this is a promising compound for the treatment of biofilm-associated fungal diseases (Yang, *et al.,* 2014).

Antioxidant properties of MLT can be beneficial for the treatment of local inflammatory lesions and to expedite the recovery process, for instance after tooth extraction or other surgical interventions in the oral cavity (Cutando, *et al.,* 2007). Also, MLT can be used to reduce inflammation as a treatment-emergent side effect (Reiter, *et al.,* 2000; Gomez-Moreno, *et al.,* 2010). Melatonin has well-known antiinflammatory and immunostimulating effects (Carrillo-Vico, *et al.,* 2005).

MLT has important physiological functions unused in dentistry. As described here, MLT can have clinical applications for the improvement of oral cavity health, which indicates that MLT can be used therapeutically, for instance, locally on bacterial or viral lesions, postoperative wounds and oral surgery, autoimmune disorders like the Sjogren syndrome, as an antiinflammatory agent on periapical lesions, on bone formation, periodontal diseases, aphthous ulceration, Lichen planus, oral cancers and even toxic effects of dental materials (Gomez-Moreno, *et al.,* 2010; Sarıtekin, *et al.,* 2019).

4. Melatonin and tooth cavities

In hamsters, which are a very seasonal species, it was observed that a larger number of cavity lesions developed in spring and summer, which see the shortest duration of nocturnal elevation in MLT, and, in turn, fewer cavities

developed in the autumn and winter, which see maximum levels of MLT. Also, considering that dental and osseous tissue material is strongly modified by cariogenic diets (Mechin, *et al.,* 1973) and that foodstuffs contain MLT, the amount of MLT in the food consumption can affect cavity incidence (Mechin, *et al.,* 1976).

5. The other effects of melatonin on the oral cavity

MLT can be used for the treatment of bacterial and viral infections in the oral cavity. Beneficial effects of melatonin as an antiviral were investigated and it was observed in various types of infection that melatonin treatment had beneficial effects on viremia and resultant mortality (Bonilla, *et al.,* 2004). On oral cavity diseases, MLT was studied in the treatment of the herpes virus in comparison with the effects of acyclovir (a common treatment used for the disease) (Nunes, *et al.,* 2008). The results showed that the efficacy of MLT in reducing the severity of the infection involved fewer side effects with almost as high efficacy as an antiviral drug. The benefits of MLT in viral infections appear to be stemming from the immunomodulatory effect in stimulation of IL-1β, which has antiviral effects, and also its antioxidant and antiinflammatory effects. Another role of MLT in viral infections could be promoting an immune system weakened by free radicals (Schwartz, *et al.,* 1996).

MLT was used in bacterial infections and it proved to be a successful therapy in various in vivo models (Reynolds, *et al.,* 2003; Nunnari, *et al.,* 2003). It exhibited action against Gram-positive and Gram-negative microorganisms both, but its efficacy was higher against Gram-negative microorganisms. It was also effective against various antibiotic-resistant bacteria strains. MLT as an antibiotic had a possible mechanism of action involving regulation of bacteria proliferation/duplication, lipid uptake reduction

(Tekbas, *et al.,* 2008) and a high capacity to bind metals, including iron (Limson, *et al.,* 1998).The antibacterial activity of MLT in the oral cavity can be beneficial in controlling periodontal disease and dental cavity induction (Cengiz, *et al.,* 2012).

6. Melatonin and herpes viral infection

MLT was compared with acyclovir in terms of its beneficial effects on herpes infections of the oral cavity. Here, MLT was demonstrated to be beneficial in the reduction of the severity of herpes at least as effectively as the prescription drug, a consistent finding with the effects MLT showed on other viral infections by reducing their severity. In these cases, the benefits of MLT appear to originate in its immunomodulatory effects in the stimulation of IL-1B, which exhibits antiviral action. The suppressive effects MLT shows on herpes can also be associated with its stimulation of NK, CD4 cells, and others. At this point, it is unknown through which mechanism MLT decreases the severity of herpes infections (Nunes, *et al.,* 2008).

A formulation with no side effects, containing 2.5 mg melatonin and 100 mg SB-73 (a mixture of magnesium, phosphate, fatty acids, and protein extracted from *Aspergillus oryzae*) was developed to support the symptom regression of a herpes virus infection. This formulation was based on published data suggesting that MLT has known immunomodulatory properties. MLT is regarded as a supplement containing natural ingredients, and it could be adjuvant in the treatment of herpes infections in individuals unable to provide prescription drugs (Boga, *et al.,* 2012).

7. Melatonin and candidiasis

It was reported that MLT, as an immunomodulator, shows protective effects against severe sepsis induced by bacterial

lipopolysaccharide in animal models. In animals with *Candida* sepsis, MLT decreased IL-6 levels and shortened recovery time. In septic rats treated with MLT, levels of TNF-α and adhesion molecules were lower compared with the levels in untreated septic rats (Yavuz, *et al.,* 2007). Based on these findings, MLT, thanks to its immunoregulatory effects, could exhibit beneficial therapeutic effects on *Candida* sepsis and conventional antimycotic treatment. MLT therefore may also be beneficial as a topical and/or systemic oral candidiasis treatment.

Results of some studies support the proposition that MLT increases phagocytic function and simultaneously reduces oxidative stress that emerges during candidiasis (Terron, *et al.,* 2003; Gomez-Moreno, *et al.,* 2010).

Kılınçel *et al.* (2019) in their study found that MLT reduced minimum biofilm eradication concentration (MBEC) and minimum inhibitory concentration (MIC) values, especially the latter. Based on the findings, MLT can be a new alternative in the treatment of *Candida* infections.

8. Conclusion

MLT contributes to protection from diseases caused by microorganisms in the oral cavity with the effects of different receptors. Based on the literature review, it was concluded that experimental evidence shows that MLT can be useful in the treatment of various common diseases of the oral cavity. Currently, however, the significance of MLT and its receptors in oral health and dentistry is less prominent.

Preliminary evidence suggests that MLT can be beneficial in the treatment of oral cavity disease.

However, from a dental perspective, it is important to provide more experimental support for the basic functions of MLT in the oral cavity.

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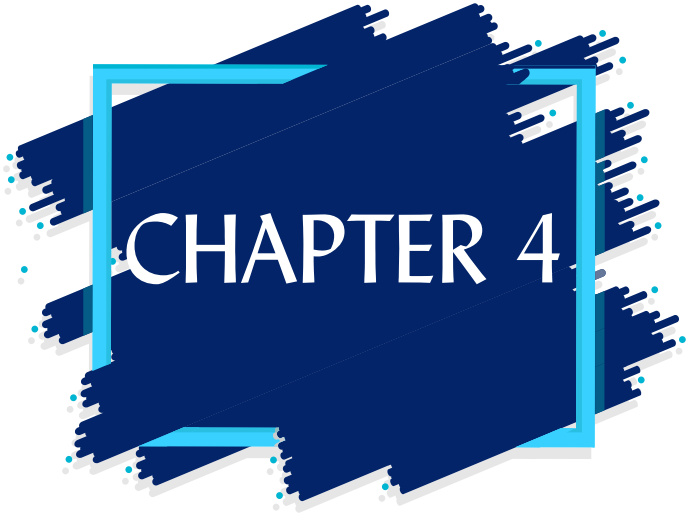
ANATOMICAL LOCALIZATIONS OF FOOTBALL INJURIES AND INVESTIGATION OF TREATMENT METHODS

Deniz ŞENOL, Şeyma TOY



ANATOMICAL LOCALIZATIONS OF FOOTBALL INJURIES AND INVESTIGATION OF TREATMENT METHODS

Deniz ŞENOL[1], Şeyma TOY[2]

Anatomical regions and rates of injuries in footballers

As a competition sport, the main goal in football is to control the ball. There is no rule that restricts man-to-man tackle and tackling with the opponent within the game rules. Therefore, in football, there is a potential risk of injury to football players. The most common injuries in footballers are lower extremity injuries; however, upper extremity injuries also tend to cause severe injury in the form of fractures and dislocation (5).

Football is a tough game and players can often get injured (6). However, football is still one of the most popular sports worldwide. Some studies have been conducted to investigate the type, location and severity of injuries in football and football players (7-10). In their study they conducted on 505 professional footballers playing actively in 2014-2015 Turkey Super League consisting of 18 teams, Bayer et al. (2017) found that 469 (92.8%) professional footballers had been exposed to a total of 2675 injuries and 40.12% of them were upper extremity, while 59.88% of them were lower extremity injuries (11). In a survey conducted with 250 athletes, Kirisci (2011) reported that 62.4% of the athletes participating in the study stated that the most risky sports branch was football. In addition, 96% of the players participating in the study stated that

1 İnönü Üniversitesi Tıp Fakültesi Anatomi Anabilim Dalı
2 İnönü Üniversitesi Turgut Özal Tıp Merkezi Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı

they experienced injury (12). According to Magnussen et al. (2010), 4,928 athletes in Norway stated that football injuries were the most common sport injuries with a rate of 42,9% (13). Dvorak et al. (2000) reported that 82% of 264 football players examined for a year had different degrees of injury (6).

According to the 1997 statistical data, 50-60% of the sports injuries in Europe occur in football. 75% of these are related to the lower extremity. Rate of ankle injury is known as 38%, knee as 17%, head as 11% and leg as 10%. Meniscus injuries seem to be associated with football because 40% of meniscus injuries in all sports are seen in football (14). In their study with 505 professional football players, Bayer et al. (2017) found that 13.6% of upper extremity injury regions were shoulder injuries, 13% were head injuries, 12.4% were finger injuries and 13.1% were elbow injuries; while 17.7% of the lower extremity injury regions were ankle injuries, 16.5% were lower leg injuries, 13.3% were upper leg injuries and 13.2% were knee injuries (11).

Upper extremity injuries are usually the result of severe falls and injuries that vary with the surface quality (15). The most common upper extremity injury in footballers is the tuberculum majus fracture of the humerus bone. Art. humeri fractures which are isolated or with rotator cuff tear are frequent. These sprains may occur with lateral impacts to the shoulder. Apart from falling, glenohumeral joint dislocation may occur with external rotation of the upper extremity of the shoulder that becomes hyperextended when throwing the ball during throw-in (16). In their study, Açak et al. (2017) found that 22.9% of upper extremity injuries of U-19 footballers were hand injuries, 12.7% were head injuries, 11% were shoulder injuries and 11% were elbow injuries; while 14.6% of U-19 footballers were

finger injuries, 14.7% were shoulder injuries, 13.5% were elbow injuries and 13.5% were head injuries (17).

The most affected joint in the upper extremity is art. cubiti. Caput radii fracture is likely to occur in this joint after elbow trauma (18). Zeren (1992) reported that 22 of 450 injuries occurred in elbow in football competitions (19).

Elbow dislocation and forearm fracture are rare in football players. Elbow sprains and contusions are common in the elbow joint. In the upper extremities, wrist injuries are mostly common after art. cubiti. Fracture in the navicular bone is rare. Dislocation and sprains of the fingers are frequent footballer injuries, especially in goalkeepers (16).

A great number of studies have examined injury risk factors, and higher age, playing time, and previous injuries have been found to increase the risk of injury (6, 20, 21). Ostenberg and Roos (2000) examined 123 female football players using a multivariate model and found that older players were at greater risk of injury (20). Previous injury has been shown to be the most important risk factor for the subsequent injury (22-24). In a study conducted with 102 players, Watson (2001) stated that the player's previous injury was an important indicator of future injury (25).

Hagglund et al. studied Swedish men's football teams in 2001 and 2002 seasons and found that players with previous hamstring injuries, inguinal damage and knee joint trauma were two to three times more likely to be exposed to the same injury in the next season. They stated that age was not associated with increased risk of injury (26). Arnason et al. reported that in 306 elite male football players in Iceland, in cases previous disability was hamstring and groin strain and ligaments of the knee

sprains, these types of injuries would be the main risk factor for subsequent injuries (23).

Football involves repetitive and asymmetric movements. Therefore, it has been emphasized in some studies that asymmetry may occur in the abdominal, lumbar and gluteal muscles. The cause of dorsalgia in athletes has been shown to be asymmetric development increasing mechanical loads in the lumbar region over time (27, 28). In a study conducted with 121 professional footballers, Cali (2010) stated that 31.4% of the football players (38 players) had diagnosed nonspecific dorsalgia problem (29).

Ekstrand and Tropp (1990) conducted a 1-year study with male footballers and found a higher risk of injury for footballers with a history of ankle problems (24).

Esenkaya et al. examined the upper extremity injuries in footballers and reported the distribution of 80 cases with injuries to the upper extremities according to anatomical regions as; wrist in 24 cases (30%), phalanx-metacarp in 19 cases (23.8%); shoulders in 14 cases (17.5%); forearm in 12 cases (15%) and elbow dislocation in 11 cases (13.7%) (5). In a study conducted with 100 professional footballers, Girgin (1991) stated that 24% of football players had shoulder injuries (30).

Ankle injuries, which are often encountered by elite footballers, are shown as the presence of experienced medical staff who know the optimal treatment and injury prevention strategies that football clubs have because of the short recovery time (8, 26, 31). When all athletes are considered, it is stated that inguinal pain is seen in 87% of football players (14).

It has been reported in many muscle activity studies that in football, muscles around art. genus show high activation

in hitting the ball, athletes' jumping and changing direction according to position (2,3).

Özdemir (2004) reported that 3-20% ligaments of the art. genus injuries occurred at lig. cruciatum posterior and 2-3% of these occurred in school-age football accidents (32). Kirisci (2011) reported that recurrence of anterior cruciate ligament injuries among athletes was the most common in footballers (48%) (12).

The risk of injury with major or minor impact on elite players within a year is known to be 50%. The materials, tools, equipment, sports environment, financial supports used during the competition are shown to cause athletes to be injured and the injury to be prolonged (33). In their study conducted on Swedish footballers, Ivarson and Johnson (2010) reported that they were injured with a rate of 65-91% in a year (34). In their study conducted on female footballers, Namlı and Şarvan Cengiz found that the body part most injured was the foot (21,2%) (35). Braham et al. (2004) stated that the most injured area in all injuries among football players was lower extremities with 28% (36). When the lower extremity injury regions of U-19 footballers were examined in Açak et al (2017)'s study, these regions were found as ankle with a rate of 20.8%, upper leg with a rate of 16.6%, lower leg with a rate of 16.5%, and knee injuries with a rate of 13.9%; while the regions injured in U-21 players were knee with a rate of 16.5%, groin with a rate of 16.3%, ankle with a rate of 15.9% and lower leg with a rate of 15.5 (17). In a similar study by Dick et al. (2007) conducted on footballers, it was concluded that the area footballers experienced injury the most were knee and foot of the lower extremity (37). Dagarov and Slanchev stated that distortions, contusions, meniscus lesions and muscle ruptures are frequently seen in football players (38).

According to a study by Carey et al, injured U-19 players stated the most (38.9%) that they stayed away from sports for 8-14 days, while they stated the least (0.8%) that they stayed away from sports for 1-3 months; U-21 players stated the most (37%) that they stayed away from sports for 2-7 days, while they stated the least (0.7%) that they stayed away from sports for 1-3 months. Lower extremity injuries often prolong medical treatment times and result in loss of time or dysfunction during play (39). Powel (1981) and Bağrıaçık & Açak (2005) defined sports injuries as cases that restrict the participation of athletes in competition or training at least one day after injury (40, 41).

Footballer injuries not only harm footballers but also adversely affect the developing football industry. Annual medical expenses of a club competing in 2014-2015 Süleyman Saba Turkey Spor Toto Super League was calculated as 12,685,120 Euros and it was determined that the health expenditures made on the value of the teams corresponded to 1.31% (42). According to the study of Junge et al., in 2003, the total of one-year medical expenses spent on football injuries in Switzerland were recorded as 145 million Swiss francs (approximately 130 million USD) and a loss of 500,000 working days was recorded. The cost of football injury in England football leagues in 1999-2000 season was determined as 118 million USD (43). In a study conducted in Australia on injury cost study in a season, the injury cost was found to be as high as 37,317,029.29 AUD $ (44).

It is noteworthy that there are few studies on “athlete health” practices, which is one of the most important components of professional football, which increases with each passing day with its social and economic dimensions and which directly concerns the health of many athletes. In order to eliminate the shortcomings felt about the health of

athletes, the existing legal regulations should be updated and the monitoring mechanisms should be made effective.

Common Injuries and Treatment Methods in Footballers

Lower extremity injuries

Anterior cruciate ligament (lig.cruciatum anterior) injury: Anterior cruciate ligament is a structure that can stabilize the movements of art. genus according to different degrees of freedom. Anterior cruciate ligament injury usually occurs as a result of sudden hyperextension, situations that can cause valgus stress, knee rotation with a sudden change of direction, or direct impact to the knee. The clinical picture progresses with a feeling of emptiness at first, followed by inability to step on the knee, pain and edema. Treatment varies according to individual's age, physical condition, and severity of the injury (45, 46).

Phase 1: It includes methods such as compression, bandaging, cold application to reduce pain and edema during the process from injury to reconstruction.

Phase 2: In this period, which includes postoperative 7-14 days, cold application, elevation and compression bandage can be applied. Angle adjustable knee brace at 0-90 ° flexion angles can be used and isometric knee extension exercises with 3 × 10 repetitions and 5 sec duration for 3-4 times a day can be applied. At the end of the 7th day, mobilization can be achieved by partial loading with the help of an angle adjustable knee brace and two crutches.

Phase 3: In this process, which includes postoperative weeks 3-5, the knee flexion can be increased to 135 ° and

mobilization can be started by placing a load first on the tip of the foot and then on the whole foot.

Phase 4: Strengthening, balance and proprioceptive exercises, fast walking, jogging and sports-oriented exercises should lead to a return to active sports. In patients with anterior cruciate ligament reconstruction, the rate of returning to sport has been reported as 66-88% (47).

Meniscus injury: One of the most frequent injuries that may occur as a result of impact, fall and excessive strain in competitions or training is meniscus injury. The type of injury, anatomical location, physical condition of the patient and repair of the meniscus are important for managing the rehabilitation process well (48). The rate of return to sport after isolated meniscus repairs is 86% for professional athletes and 90% for active individuals who do regular sports even though they are not professional.

Maintenance phase: During this 0 - 6 week period, the aim can be to protect the surgery, to reduce effusion and to complete the normal joint movement.

Weight transfer phase: In this phase between 7-9 weeks, the aim can be full weight transfer, to improve walking pattern and increase standing tolerance.

Endurance phase: In this period, the aim can be to squat with knee flexion not exceeding 70°.

Strengthening phase: In this phase, the aim should be more than 80% quadriceps index and Y balance test should be targeted to be <8 cm compared with the other side.

Return to Sport: The quadriceps index should be targeted to be> 90%, and the Y balance test should be <5 cm compared to the other side (49).

***Achilles tendon rupture*:** A degenerated Achilles tendon breaks when it encounters an overload. This injury, most commonly seen in men aged 30-40, occurs frequently during a football match. The rupture site is usually 4-5 cm proximal to the tendon's adherence to the calcaneus, where the tendon has the weakest blood supply. If left untreated, Achilles tendon rupture leads to a significant decrease in the strength of the tendon, that is, the ankle plantar flexion strength. There is a 10 to 20% risk of rupture after a conservative treatment with a cast fixation over the knee for three months. Rather than accepting this high risk in athletes, surgical treatment is recommended to every possible patient. Post-operative fixation is performed with a knee cast or device for a period of time that the surgeon deems appropriate, especially ankle dorsiflexion is prevented. Return to sports after surgery is allowed at the earliest 6 months. Return to sport rate is close to 100% (50).

***Foot - ankle injury*:**

In studies conducted, 25% of the injuries in all sports branches are foot and ankle injuries and 85% of these injuries are lateral collateral ligament injuries. 30.2% of the problems accompanying injuries are pain, 20.4% are instability, 18.3% are crepitation, 16.5% are muscle weakness, 14.6% are stiffness and 13.9% are edema (51, 52). Ankle injuries are common and are highly likely to recur. The treatment of foot-ankle injuries varies according to the severity of the injury. In addition to the many treatment programs implemented, a well-planned exercise program increases the effectiveness of the treatment. Both during and after treatment, external supports such as elastic bandage, banding and orthosis can be used to support the treatment and reduce the risk of re-injury to the athlete. A good external support should not limit the

movement of the ankle and increase ankle stability, nor should it adversely affect the athlete's physical form (53).

Upper Extremity Injuries

***Humerus shaft fracture*:** Humeral fractures occur especially after sprains and bending injuries. Pain in the arm region, loss of movement in the shoulder and elbow joints, and shortness of the humerus neck are observed. It can be treated conservatively but there are also situations in which football players need to be followed up with surgical treatment to accelerate the return to competitions.

Despite conservative treatment; Surgical treatment of fractures with a shortening of more than 3 cm, rotation of more than 30º, or angulation of anterior-posterior / lateral planes above 20º is recommended (54, 55).

Ligament and capsule injuries around the elbow: It can occur with sudden traumas in football players, as well as with repeated overuse. The first treatment option for recurrent valgus-extension injuries is splinting, ice application and limitation of sportive activities. Full ruptures cause a continuing drop in sensation, throwing power and speed, especially in professional athletes. Reconstruction options with tendon graft are used in surgical treatment.

In the conservative follow-up of partial tears, the rate of return to the same level of sport is 93%, while the rate of return to sports in the treatment of complete tears with surgery is 75%, and return to the same level of sports is 63% (55).

***Hand tendon injuries*:** Hand injuries are common injuries in all kinds of sporting activities. The majority of these injuries are soft tissue injuries. The tendon injuries of

the hand have an important place among soft tissue injuries, which jeopardizes the functional capacity of the athlete. Depending on the injury mechanism, tendon injuries are divided into two as overuse and traumatic injuries. Athletes who engage in football, basketball, handball and fight sports are more likely to experience traumatic injuries. Rehabilitation can be done with bandages, splints and resting (56).

Phalanx fractures: Phalanx fractures are common fractures of the upper extremity in footballers. Especially distal phalanx fractures constitute 45-50% of all hand fractures. Although conservative treatment is generally preferred, surgical treatment may be required in athletes considering the length of splinting period (4-6 weeks). Surgical treatment is inevitable if the fracture is more than 1/3 of the joint and there is subluxation of the joint. Surgical treatment should be performed with closed methods (57).

Depending on the severity of the injury, athletes stay away from sports and training programs for a certain period of time following injury. These periods negatively affect the physical characteristics and performance of the athlete. Rehabilitation programs aim to minimize these losses and enable the athlete to return to sport in the earliest period. Rehabilitation programs will provide more effective results and accelerate the individual's return to sports when they are tailored to the person's age, gender, physical condition and sports.

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INFLAMMATION IN PATIENTS WITH INSULIN RESISTANCE

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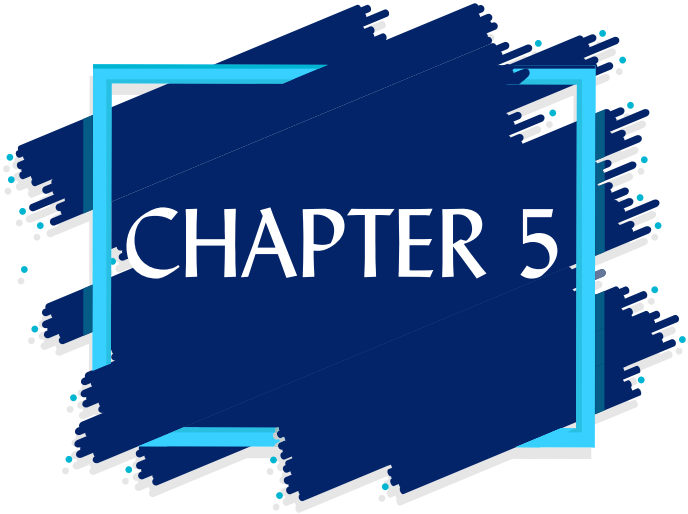

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INFLAMMATION IN PATIENTS WITH INSULIN RESISTANCE

Gülin ÖZTÜRK ÖZKAN[1]

INTRODUCTION

Insulin resistance is defined as reduction of the response of peripheral tissues to insulin movement [1]. Prevalence of obesity and insulin resistance has been significantly increasing in the world [2]. One of the most important reasons is seen as sedentary lifestyle and the change in dietary habits [3]. The studies conducted within last 10 years have revealed that inflammatory reactions have played a critical role in the formation mechanisms of insulin resistance and Type 2 diabetes mellitus [3]. Insulin resistance is examined as a chronic inflammatory disease [1]. In the patients with insulin resistance, interleukin-1 (IL-1), interleukin-6 (IL-6), C reactive protein (CRP) and tumor necrosis factor-α (TNF-α) levels that are the inflammation markers are high. The purpose of this study is to determine the presence of inflammation in the patients with insulin resistance.

Definition of Insulin Resistance

Insulin resistance is defined as the reduction of insulin movement on the peripheral tissues [1]. Also, insulin resistance is defined as the need to more insulin than normal in order to develop a normal response [4]. Hyperinsulinemia occurring in insulin resistance causes the increase in insulin release depending on the grade of insulin sensitivity. High insulin level reduces insulin efficiency and thus improves

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the insulin resistance [5]. As a result, hyperinsulinemia and glucose intolerance occur and trigger Type 2 diabetes [6].

Although the molecular mechanism causing insulin resistance cannot be understood exactly, it is suggested that adipose tissue accumulation is closely correlated with the development of insulin resistance. In the recent studies; it has been determined that obesity and insulin resistance are related to low-grade of chronic systemic inflammation [7].

The correlation of inflammation and obesity

In obesity, a low-grade proinflammatory situation occurs [8]. Obesity-correlated chronically low-grade inflammation is defined as inflammatory markers and the increase in systemic concentrations of cytokines. It is shown that chronically low-grade inflammation develops a correlation between obesity and insulin resistance [9]. Proinflammatory cytokines released from the adipose tissue contribute to obesity-related morbidity. In obese patients, serum inflammatory marker levels increase and they are correlated with the grade of insulin sensitivity [10].

Role of inflammation in insulin resistance

Insulin performs the role of blood glucose regulation by stimulating the hepatic endogenous glucose production and the glucose intake in the muscles and adipocytes. Insulin shows activity by binding to the insulin receptor on the cell surface and through the activation of this receptor [11]. Binding of insulin to the receptor activates the cases including the interaction and phosphorylation of many molecules. Stimulated insulin receptors phosphorylate itself and various substrates [11]. These are insulin receptor substrates. Insulin receptor substrate (IRS) proteins are the essential coupling proteins mediating insulin communication in insulin-sensitive various tissues

[12]. Key molecules on the insulin signal pathway are insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2)[11]. Insulin receptor is a transmembrane glycoprotein consisting of 2 extracellular α sub-groups and 2 transmembrane β sub-groups. α sub-group of the receptor includes an insulin binding region [12]. Activation of the insulin receptor requires the tyrosine autophosphorylation of 3 tyrosine residues. In order for insulin to function, tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2) proteins is required[11].

In addition to tyrosine autophosphorylation, insulin receptors are also subject to serine/threonine phosphorylation[11]. In insulin resistance, a decrease in tyrosine phosphorylation of IRS-1 and an increase in serine/threonine phosphorylation occur[11,13]. In some studies, it was shown that tyrosine kinase activity of insulin receptor decreased as a result of serine/threonine phosphorylation [13]. Serine phosphorylation of insulin receptor substrates causes degradation in insulin communication. This phosphorylation prevents the binding of insulin receptor substrates to insulin receptors. Thus, serine/threonine phosphorylation of IRS-1 may degrade the insulin movement. As a result, it causes a decrease in the flow [14].

Inflammatory mediators

Essential inflammatory mediators participating in the insulin resistance formation process are given below.

TNF-α (Tumor Necrosis Factor-α)*:* TNF-α is a proinflammatory cytokine and mediates an inflammatory response [15]. TNF-α acts a key role in the regulation of adipose tissue metabolism. TNF-α contributes in clinical and metabolic irregularities occurring in insulin resistance correlated with obesity. TNF is an essential inhibitor of

insulin sensitivity. Insulin sensitivity develops by the serine phosphorylation of key proteins participating in the communication process including insulin receptor and insulin receptor substrate 1 [16].

TNF-α increases the serine phosphorylation of IRS-1. This mechanism reduces tyrosine phosphorylation of insulin receptor. Serine phosphorylation of IRSs causes a degradation in normal insulin response [17].

IL-6 (Interleukine-6): Adipose tissue releases IL-6 in non-inflammatory situations. IL-6 is one of the proinflammatory cytokines that correlated with insulin resistance in circulation [18]. IL-6, like TNF-α, is released by the adipose tissue. In obesity, IL-6 level in adipose tissue has excessively increased. IL-6 release is triggered by TNF-α. Increased IL-6 level shows the development of Type 2 diabetes. IL-6 plays an important role in hepatic insulin resistance of obesity. IL-6 may inhibit the signal transfer of insulin receptor. IL-6 realizes this via the deterioration which insulin receptor substrate, ubiquitin, is a mediator [18].

IL-1β (Interleukine-1β): IL-1β is one of the essential proinflammatory cytokines [19]. It acts as a key regulator in the inflammatory response of the body. It is performed by the monocytes and macrophages. It is produced in infection and injury situations [16]. In obesity and insulin resistance, an increase occurs in the level of this cytokine [20]. In insulin-sensitive organs, the production of IL-1β by macrophages plays a role in the formation of inflammation[16].

CRP (C-reactive Protein): CRP is a sensitive indicator for systemic inflammation. Low-grade chronic inflammation is correlated with increased serum CRP level [21]. In obese patients, it is reported that CRP level has increased [22]. Body weight loss causes a decrease in

CRP level [23]. It is shown that CRP level is correlated with glycemic control. There is a correlation between increased CRP level and insulin resistance [24].

METHODS

This study was conducted with participation of 53 female patients aged between 30 and 50 years who applied to Internal Medicine Outpatient Clinic, Haydarpaşa Numune Training and Research Hospital. The patients included in the study were selected among the people who applied to the internal medicine outpatient clinic for the purpose loss of weight, were diagnosed with insulin resistance for the first time, had a BMI between 30 and 40 kg/m^2, and had no other diseases other than hyperlipidemia.

Anthropometric Measurements

Heights and body weights of the patients included the study were measured and their body mass indexes (BMI) were calculated. These measurements were performed by using a height-measuring digital scale at Haydarpaşa Numune Training and Research Hospital Dietetic outpatient clinic.

Body mass index was calculated as shown below [25].

BMI = Body weight-kg/(Height -m)^2

Also by using a body composition analysis device, body fat amount and body fat percentage were measured. In order to determine these values, Tanita BC 418 Segmental Body Analysis device at Haydarpaşa Numune Training and Research Hospital Dietetic outpatient clinic was used. While performing this measurement, attention was paid to the patients to be hungry, not drink water, not perform any physical activity, and not take caffeine and alcohol on the last day.

Waist and hip circumferences of the patients included in the study were measured by the researcher and waist/hip ratios were calculated.

Biochemical parameters

Biochemical findings (glucose (fasting), insulin (fasting), glucose (postprandial) and insulin (postprandial) of the patients regarding their clinical insulin resistance and their inflammation findings were examined. Therefore, blood was taken from the patients after 12-hr fasting and then they were asked to have a breakfast. Blood was taken again 2 hours after the breakfast. These examinations were requested as a routine procedure from all the patients applied to the outpatient clinic for the purpose of losing weight.

All the biochemical measurements were performed at Haydarpaşa Numune Training and Research Hospital, Biochemistry Laboratory.

By using the fasting glucose and fasting insulin values; HOMA-IR value, that is the insulin resistance index, was calculated by the researches as follows [26].

HOMA-IR = [Glucose (fasting) (mg/dL) x Insulin (fasting) (μIU/ml)] / 405

Normal values of the biochemical parameters of insulin resistance are given below.

Glucose (fasting): 74-110 mg/dL

Glucose (postprandial): <140 mg/dL

Insulin (fasting): 1.9-23 μIU/mL

Insulin (postprandial): 16-161 μIU/mL

HOMA-IR: < 2.5

Inflammatory Parameters

In order to assess the inflammation situation, CRP, TNF-α, IL-1 and IL-6 values were examined. Therefore, approximately 10 mL blood was taken from the patients. These parameters were examined at Haydarpaşa Numune Training and Research Hospital, Microbiology laboratory. Among the said values, CRP is routinely examined and TNF-α, IL-1, IL-6 are not routinely examined. For this study, Orgenium brand TNF-α, IL-1 and IL-6 kits were brought by the researcher from Finland.

Normal values of inflammation findings are given below.

CRP: 0.0-0.8 mg/dL

TNF-α: 0-16 pg/mL

IL-1β: 0-12 pg/mL

IL-6: 0-8 pg/mL

Statistical evaluation of the data

SPSS statistical package program was used to assess the data. More than one method was used for assessing the data obtained as a result of the study. Mean and standard deviations of biochemical test results were calculated. Assessment regarding the presence of a correlation between these variables was performed by using the correlation analysis, one-way analysis of variance and Fisher's exact chi-square method.

This project has been evaluated by the Hacettepe University Scientific Research Evaluation Commission and approved by the decision of LUT 10 / 39-15.

RESULTS

This study was conducted to determine the presence of inflammation in the patients with insulin resistance. 53 female patients aged between 30 and 50, who had a BMI value of 30 kg/m^2 and more and had no disease other than insulin resistance and hyperlipidemia, were included in the study.

Table 1 shows the results regarding the assessment of inflammation findings of the patients according to the age groups. In the patients included in this study, it was determined that among the inflammation findings, CRP was 0.5±0.3 mg/dL, TNF-α was 239.0±218.7 pg/mL, IL-1β was 82.7±14.8 pg/mL and IL-6 was 21.4±69.5 pg/mL. When these results were compared with normal values, it was observed the CRP was within normal limits and TNF-α, IL-1β and IL-6 values were above the limit.

It was found that CRP, TNF-α, IL1β and IL-6 values in the blood of the patients did not vary based on age (p=0.835, p=0.894, p=0.617, p=0.316).

Table 1. *Mean and standard deviation values of the inflammation findings of the patients in terms of the age groups*

Inflammation findings	N=53 X ± SD	Minimum	Maximum	30-35 years N=18 X±SD	36-40 years N=12 X±SD	41-45 years N=8 X±SD	46-50 years N=15 X±SD	P
CRP (mg/dL)	0.5 ± 0.3	0.0	1.5	0.5±0.4	0.5±0.3	0.6±0.4	0.5±0.3	0.835
TNF-α (pg/mL)	239.0 ±218.7	8.6	500.0	273.8±242.9	207.7±227.9	173.8±276.5	261.9±164.9	0.894
IL-1β (pg/mL)	82.7 ± 14.8	7.8	500.0	45.0±114.6	104.7±154.3	88.8±170.3	107.2±172.5	0.617
IL-6 (pg/mL)	21.4 ± 69.5	7.8	500.0	14.3±27.5	54.5±141.3	12.8±14.0	8.0±0.9	0.316

¶ One-way analysis of variance (ANOVA)

*p<0.05

Table 2 shows the findings related to the correlation between the biochemical findings of the patients regarding insulin resistance (fasting glucose, postprandial glucose, fasting insulin, postprandial insulin, HOMA-IR) and their inflammation findings (CRP, TNF-α, IL-1, IL-6). When the correlation between the biochemical findings on insulin resistance and inflammation findings of the patients was examined, no correlation was found between fasting glucose and CRP, TNF-α, IL-1 and IL-6 (p=0.086; p=0.473; p=0.094; p=0.242) and between postprandial glucose and CRP, TNF-α, IL-1 and IL-6 (p=0.645; p=0.392; p=0.687; p=0.724). No correlation was found between the fasting insulin values and CRP, TNF-α, IL-1 and IL-6 values of the patients (p=0.267; p=0.795; p=0.267; p=0.536) and also between the postprandial insulin and CRP, TNF-α, IL-1 and IL-6 (p=0.636; p=0.072; p=0.135; p=0.742). Also, no correlation was found between HOMA-IR and CRP, TNF-α, IL-1 and IL-6 (p=0.058; p=0.587; p=0.291; p=0.352).

Table 2. *Assessment of the correlation between the biochemical findings on insulin resistance and inflammation findings of the patients*

Biochemical findings on insulin resistance	***CRP***		***TNF-alpha***		***IL-1***		**IL-6**	
	r	***P***	***r***	***P***	***r***	***P***	**r**	**P**
Fasting glucose	0.238	0.086	0.154	0.473	0.232	0.094	0.164	0.242
Postprandial glucose	0.065	0.645	0.183	0.392	0.057	0.687	0.050	0.724
Insulin, fasting	0.155	0.267	0.056	0.795	0.155	0.267	0.087	0.536
Insulin, postprandial	-0.067	0.636	0.374	0.072	0.208	0.135	0.046	0.742
HOMA-IR	0.262	0.058	0.117	0.587	0.148	0.291	0.130	0.352

¶ Correlation Analysis

* $p<0.05$.

No statistically significant correlation was found between fasting glucose, postprandial glucose, fasting

insulin, postprandial insulin and HOMA-IR values and CRP, TNF-α, IL-1 and IL-6 values of the patients.

The correlation between the anthropometric measurements and inflammation findings of the patients was assessed in Table 3.

When the correlation between BMI, fat amount, fat percentage, waist circumference, waist circumference, waist/hip ratio and CRP, TNF-α, IL-1 and IL-6 was assessed, a positive and weak correlation was found between BMI and CRP (p=0.004; r=0.391). It was observed that there was a positive weak correlation between the body fat amount and CRP (p=0.018; r=0.324). Also, a positive weak correlation was found between the body fat percentage and CRP (p=0.001; r=0.439). However, no correlation was found between the body fat percentage and TNF-α, IL-1 and IL-6 (p=0.660; p=0.980; p=0.220). A positive weak correlation was found between the waist circumference measurement and CRP (p=0.015; r=0.333).

Table 3. *Assessment of the correlation between the anthropometric measurements and inflammation findings of the patients*

Anthropometric measurements	***CRP***		***TNF-alpha***		***IL-1***		**IL-6**	
	r	***P***	***r***	***P***	***r***	***P***	***r***	***P***
BKI (kg/m²)	0.391	0.004*	0.001	0.995	0.112	0.426	0.196	0.160
Body fat (kg)	0.324	0.018*	0.052	0.809	0.068	0.626	0.173	0.215
Body fat (%)	0.439	0.001*	-0.095	0.660	0.001	0.980	0.171	0.220
Waist circumference (cm)	0.333	0.015*	0.026	0.906	0.014	0.920	0.079	0.576
Hip circumference (cm)	0.223	0.109	0.049	0.818	0.159	0.254	0.190	0.173
Waist/Hip	0.138	0.325	-0.092	0.668	-0.146	0.297	-0.028	0.844

¶ Correlation Analysis

* $p<0.05$

A significant correlation was determined between BMI, fat amount, fat percentage, waist circumference

measurements and CRP of the patients (p=0.004; p=0.018; p=0.001; p=0.015) and the correlations between CRP and other findings were not statistically significant.

DISCUSSION

There is a correlation between body weight gain, insulin release and insulin sensitivity [27]. In recent years, evidences have been obtained regarding the correlation between the metabolic problems such as Type 2 diabetes and cardiovascular diseases and a part of adipose tissue endocrine function. Adipose tissue cells release bioactive substances called as adipokines [28]. Within the adipose tissue, inflammatory adipokines are released from the non-fat cells. The said proteins play important endocrine roles in the regulation of appetite, blood pressure and glucose balance. Increased adiposity causes low level of chronic inflammation in adipose tissue. Adipokines stimulate inflammation [28]. Inflammation causes an increase in the production of proinflammatory cytokines such as monocyte chemotactic protein-1 (MCP-1), IL-6, TNF-α, plasminogen activator inhibitor-1 (PAI-1) and angiotensin II and a decrease in production of anti-inflammatory adipokines such as adiponectin [27].

Adipokines are the proteins affecting insulin sensitivity. Factors released from the adipose tissue can degrade the insulin communication that includes the glucose balance and lipid metabolism and changes in the processes where the insulin is a mediator [28]. Thus, it may help insulin resistance [9].

CRP, a common indicator of inflammation, is an acute phase reactant produced in the liver [29]. It is reported that CRP level increases in obese patients [22]. A correlation is reported between the increased CRP level and insulin resistance. In the study by Promintzer et al. [24], it was

determined that increased CRP level was correlated with insulin level. In the study by Belhayara et al. [30] it was specified that there was a positive correlation between insulin resistance and CRP. In a study, high-sensitivity C-reactive protein (hs-CRP) level was found to be higher in individuals with insulin resistance than in individuals without insulin resistance [31]. In another study by Başyiğit et al. [32] it was shown that there was no difference between the CRP levels of the patients with low and high HOMA-IR values. Similarly, in this study, no statistically significant correlation was found between fasting glucose, postprandial glucose, fasting insulin, postprandial insulin and HOMA-IR values and CRP.

TNF-α is an inflammatory cytokine and it is produced by the macrophages in the adipose tissues. It needs local inflammatory cells for activation [33]. NFkB stimulates TNF-α production. It has been specified that the increase in the synthesis and release of TNF-α by the adipose tissue plays a role in the correlation between obesity and insulin and inflammation. TNF-α could change the glucose balance of the whole body and it is included in obesity and the insulin resistance developed related to obesity. The level of TNF-α in the circulation increases in obese patients. TNF-α receptors in the circulation are in correlation with BMI. Its level decreases after body weight loss. In the said patients, excess TNF-α is produced in adipose tissue [34]. In this study, the mean TNF-α values of the patients was determined as 239.0±218.7 pg/dL (Table 1). This value is quite higher than normal limit. This result supports that TNF-α level increases in the patients with insulin resistance.

During obesity, IL-1 has a pathogenic role in the adipose tissue. It is asserted that IL-1β can promote the production of other proinflammatory cytokines including IL-6 [35]. In this study, it was determined that mean IL-1β of the

patients was 82.7±14.8 pg/mL (Table 1). This value was above the normal limit. In the study by Nov et al. [36], it was shown that IL-1β level increased in obesity. The results of these two studies support each other. Hyperglycemia improves the production of IL-1β [37]. The increase of the IL-1β production in adipose tissue contributes to the development of insulin resistance [34,35].

IL-6 is a cytokine produced by various cells [34]. IL-6 is produced by the pancreas cells, adipose tissue cells and skeletal muscle cells and leucocytes that play a role in the glucose balance. It is shown that this cytokine is critically correlated with metabolism and inflammation. Level of IL-6 in the circulation and its production in adipose tissue increase in obesity [34]. Its release from visceral adipose tissue is 2-3 times greater than subcutaneous release. IL-6 is in a strong correlation with insulin resistance [34,35]. Increased IL-6 level causes a degradation in insulin sensitivity [38]. In this study, it is seen that mean IL-6 values of the patients was 21.4±69.5 pg/mL (Table 1.). This value was more than the normal limit. Also, there are researches supporting this study. IL-6 levels of individuals with metabolic syndrome and healthy individuals were compared in a study. The mean IL-6 of the patients with metabolic syndrome and the IL-6 mean of individuals without metabolic syndrome were 7.01 ± 0.51 pg/mL and 4.06 ± 0.27 pg/mL, respectively. IL-6 levels were found to be increased in individuals with metabolic syndrome ($p < 0.001$) [39].

In this study, mean and standard deviation values of the inflammation findings were assessed according to the age groups of the patients, as well (Table 1). According to the age groups, no statistically significant difference was observed in IL-1β, IL-6, TNF-α and CRP levels ($p > 0.05$).

When the correlation between the biochemical findings on insulin resistance and inflammation findings was examined in this study, it was concluded that CRP, TNF-α, IL-1, IL-6 were not correlated with fasting glucose, postprandial glucose, fasting insulin, postprandial insulin and HOMA-IR (Table 2.). The fact that there was no correlation between IL-6 and glucose, insulin and HOMA-IR might be associated with the fact that IL-6 takes part in hepatic insulin resistance. IL-1 affects mainly the cytokine activation and the production of acute phase proteins. For example, IL-1 takes place in the production of IL-6 together with TNF-α [40]. Due to its indirect effect, the correlation might not have been determined between glucose, insulin and HOMA-IR in this study.

In the present study, a correlation was found only between BMI, body fat amount and body fat percentage and CRP values of the patients. There were a positive weak correlation between BMI and CRP ($p=0.002$; $r=0.399$); a positive weak correlation between the body fat amount and CRP ($p=0.001$; $r=0.388$), and a positive weak correlation between the body fat ratio and CRP ($p=0.001$; $r=0.460$). It was observed that there was no correlation between CRP and other variables. A reason for the correlation only between CRP and anthropometric measurements can be that the insulin resistance has not progressed in the patients yet. If no precaution is taken, it is thought that deteriorations may occur in other inflammation findings.

As a result of this study, when the inflammation findings of the patients were compared to normal values; it was found that CRP levels were normal and TNF-α, IL-1β and IL-6 levels were high. The correlation between the insulin resistance findings (fasting glucose, postprandial glucose, fasting insulin, postprandial insulin and HOMA-IR) and inflammation findings (CRP, TNF-α, IL-1, and IL-6) of the patients was not found as statistically

significant. It was determined that there were a positive weak correlation between BMI and CRP of the patients (p=0.004; r=0.391), a positive weak correlation between the body fat amount and CRP (p=0.018; r=0.324); and a positive weak correlation between body fat percentage and CRP (p=0.001; r=0.439).

According to the results of this study; an increase occurred in the inflammation markers of the patients with insulin resistance. The patients included in the study were selected among the patients who were newly diagnosed with insulin resistance. The disease was just in the onset phase. Thus, a significant correlation may not be found between insulin resistance indicators and inflammation indicators. In addition, the female gender of all the patients included in the study may also affect the results. Low visceral fat mass and efficiency of estrogen on insulin sensitivity in female may be effective regarding the absence of a significant correlation between the insulin resistance indicators and inflammation indicators. Inflammation can be seen in obese patients. Inflammation is closely correlated with the insulin resistance. Thus, providing the body weight control in the patients with insulin resistance may reduce the risk for development of Type 2 diabetes. Also, giving an anti-inflammatory support to these patients may provide a positive contribution to the treatment of insulin resistance.

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THE VALUE OF BIOCHEMICAL, HORMONAL AND COAGULATION RELATED TESTS IN THE DIAGNOSIS OF MOL HYDATIFORM

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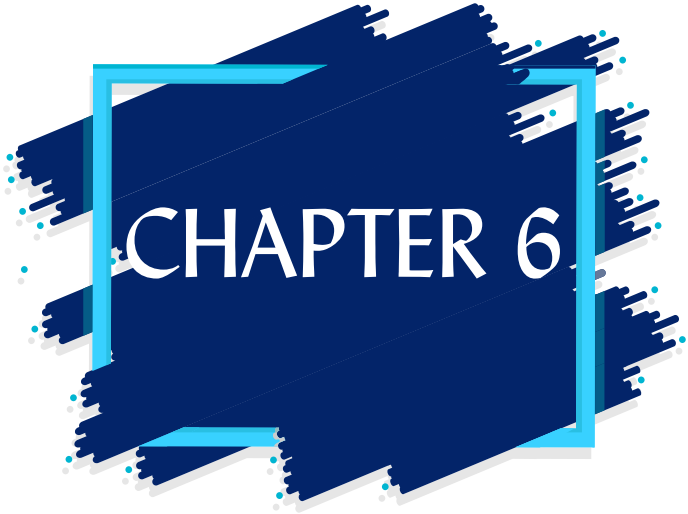

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THE VALUE OF BIOCHEMICAL, HORMONAL AND COAGULATION RELATED TESTS IN THE DIAGNOSIS OF MOL HYDATIFORM

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INTRODUCTION:

Gestational trophoblastic disease (GTD) is the general name given to a group of diseases which are characterized by abnormal proliferation of trophoblasts. Gestational trophoblastic diseases are classified by their to anatomoclinical characteristics according to the World Health Organization (de Almeida et al., 2011). Gestational trophoblastic diseases include malignant forms such as life-threatening choriocarcinoma and benign forms such as mole hydatiform (MH), revealing heterogeneity of the disease (Figure 1).

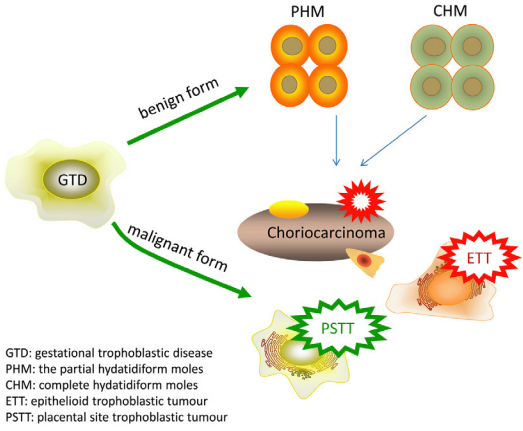

Figure 1: *Forms of gestational trophoblastic diseases (Ning et al., 2019)*

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The history of gestational trophoblastic diseases is very old. In ancient Greek medical texts, abnormal pregnancies of unknown cause are mentioned. In 400 B.C., Hippocrates described the mole hydatorm as the drop structure of the uterus (Ober and Fass, 1961). The researches about histopathology of GTD and clinical-pathological classifications date back to the 19th and 20th centuries (Hammond et al., 1992; Paradinas and Elston, 2003).

The incidence of gestational trophoblastic diseases varies considerably between regions. The incidence of GTD in the United States has been reported to be 1 in 1500 pregnancies (Garner et al., 2007). In a study conducted in the United Kingdom in 1986, the prevalence of GTD was reported to be 1.5 / 1000 pregnancies (Bagshawe et al., 1986); while in another study, the incidence of mole pregnancy in Asian and non-Asian populations was investigated and the risk was reported to be 1.9 times higher in Asian populations (Tham et al., 2003). For Australia and Europe, the incidence of MH was reported to range from 0.57 to 1.1 per 1000 pregnancies, while this rate was reported as 2/2000 for southeast Asia (Atrash et al., 1986). In our country, the incidence of GTD is reported as 0.38 per 1000 births (Ozalp et al., 2014). In the study of Adalı et al. -where the current study was conducted- the prevalence of MH was reported to be 6.9% among all the termination materials (Adalı et al., 2018).

MH the benign part of the disease group (Leenharattanarak and Lertkhachonsuk, 2015) is an abnormal pregnancy with trophoblast hyperplasia and hydropic chorionic villi. Risk factors for MH (Nadhan et al., 2017), which make up about 80% of gestational trophoblastic diseases, include socioeconomic status, blood group, age of menarche, maternal age, parity, molar

pregnancy story, genetic factors, malnutrition, parasites and infections (Ghaemmaghami et al., 2006).

Considering its histopathological and genetic characteristics, MH is divided into two as complete mole hydatiform (CMH) and partial mole hydatiform (PMH). In cases where myometrial invasion is observed, it is accepted as invasive molar hydatiform (IMH) regardless of its type. There are also differences in the etiologic factors between CMH and PMH. While no relationship is reported between maternal age (Parazzini et al., 1986) and nutritional factors and PMH, it has been suggested that oral contraceptive use and menstruation irregularities may have an effect (Berkowitz et al., 1995).

Although it was observed that there was a big difference between the prevalence values during the periods when karyotype determination possibilities were limited, it was accepted that the genetic gender was mostly female (XX) in molar pregnancies (Elston, 1970). As the technical possibilities increased, it was found that the majority of CMH cases were in the structure of 46, XX (Vassilakos et al., 1977). Similarly, as the morphological classification was insufficient, cytogenetic studies on partial mole were insufficient. However, many studies have found a relationship between hydropy and triploidy (Van de Kaa et al., 1993; Schlegel et al., 1966); Szulman and Surti reported that the majority of PMH cases triploid karyotype (Szulman and Surti, 1978a). Figure 2 illustrates the karyotypic schematization of CMH and PMH (Stevens et al., 2015). When it comes to IMH, pathogenesis of myometrial invasion in IMH is not clear. While there is no correlation between the length of stay of MH in uterus and the development of invasion and persistent disease, it is stated that there is a relationship with metastasis formation (Paradinas et al., 1996; Benirschke et al., 2000). There are studies reporting that disruption of the mechanisms

controlling the invasion in the implantation site also leads to the development of IMH (Paradinas and Elston, 2003).

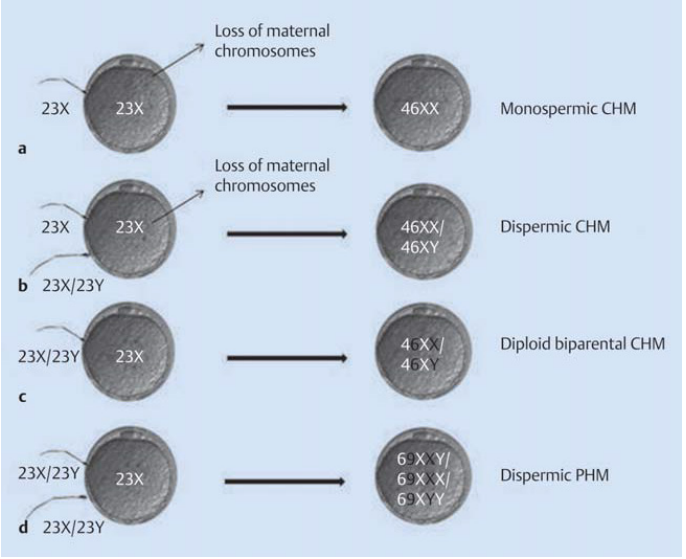

Figure 2: *Genetic structure of MH (Stevens et al., 2015)*

Histopathologically, it is characteristic that in the second and third trimesters of MH, chorionic villi in the mold turn into vesicles, macroscopically larger uterus, grape bunch appearance within the uterus and no molar tissue-related fetus is observed (Hammond et al., 1992; Paradinas and Elston, 2003; Rustin, 1997; Elvin et al., 2006; O'Quinn and Barnard, 1991). In addition, with the increasing sensitivity in ultrasonography and patient follow-up, it can be noted that the gestational week at the time of diagnosis may have decreased to an average of 9.4-12. This causes the absence of the classical macroscopic appearance and if the microscopic evaluation is not performed, the cases may not be diagnosed (Paradinas and Elston, 2003; Benirschke et al., 2000; O'Quinn and Barnard, 1991; O'Quinn and Barnard, 1991). Microscopically, findings of CMH can be summarized as proliferation of proliferating

cytotrophoblastic or syncytiotrophoblastic elements, villous stromal edema, avascular villi and absence of non-villous gestational tissues (Elvin et al., 2006; O'Quinn and Barnard, 1991). The histopathological diagnosis of the partial mole is more challenging. One of the reasons for this is the monitoring of excess trophoblast in a small number of sections and / or in a small area (Szulman and, Surti U. 1978b; Thaker and Berlin. 2004). Another reason is that both cytotrophoblast and syncytiotrophoblast excess are observed in CHM, whereas syncytiotrophoblast excess is generally observed in PMH. Another important point is that the excess trophoblast seen in PMH should be differentiated from excessive trophoblastic tissue in early abortion. Histopathologically IMH can be defined as the presence of the villus structure of the partial or complete mole in the myometrium or its vascular spaces.

Clinically, vaginal bleeding is the most common finding in MH cases and is observed in 72-84% of cases (Singer et al. 2002.). Vesicle fall with bleeding is also observed as a common condition (Rustin, 1997). Ultrasonographic examination revealed multiple echoes within the uterine cavity, increased transverse diameter of the gestational sac, and large uterine dimensions compared to gestational week. Since beta hCG is one of the most characteristic features of trophoblastic tissue, beta hCG level has a very important role in the diagnosis, treatment and follow-up of the disease (Indraccolo et al., 2006). In most cases, beta-hCG levels begin to decrease following molar curettage and return to normal values at an average of 9 weeks (Soper et al., 2004). If beta-hCG does not decrease or increase, this situation indicates that there are tumor cells that persist (O'Quinn and Barnard, 1991). Another sign of gestational trophoblastic diseases is preclampsia and almost all of the cases of preclampsia consist of patients with high uterine size and very high levels of hCG. For this reason, the possibility of GTD should be

evaluated in pregnant women diagnosed with preclampsia in the first half of pregnancy. Hyperemesis gravidarum is also observed with increased frequency in patients with large uterus and hCG levels compared to gestational week (Hou et al., 2008). As a result of dose-dependent thyroid-stimulating hormone (TSH) suppression (Lockwood et al., 2009) due to thyrotropic effect of hCG at high concentrations; tachycardia, high body temperature, tremor and hyperthyroidism may be observed and the diagnosis is made with free thyroxine and triiodothyronine, which are detected high in serum. Thyroid storm, which may be fatal in GTD, is characterized by hyperthermia, delirium, convulsion, tachyarrhythmia, high-output heart failure or cardiovascular collapse (Jeffers et al., 1993).

It is reported that approximately 10-20% of CMH and less than 5% of PMH's develop into post-molar gestational trophoblastic neoplasia (GTN) requiring chemotherapy (Al-Khan et al., 2012). Therefore, accurate and early diagnosis of CMH and PMH is also important for early diagnosis of GTN. Many studies in the United States, the United Kingdom and Japan have shown that this rate is approximately 17-33%, and the probability of developing GTN following PMH has been significantly lower (Paradinas et al., 1996). In the study where 4-year neoplasia assessment was performed in the city of the presented research here, the frequency of GTN was reported as 0% (Adali et al., 2019). Although the mechanism for invasive or choriocarcinoma arise from MH is still unclear, it is thought to be multifactorial (Al-Khan et al., 2012). Although the overall survival in gestational trophoblastic neoplasms is as high as 90%, a 10% fatality rate, especially from choriocarcinomas, is observed (Al-Khan et al., 2012).

In general, the diagnosis of MH is important for many reasons, primarily because of the risk of fatality. Fatality

and persistence are the main focus of the studies and the diagnostic approach is more limited in terms of searches (Yang et al., 2002; Yang et al., 2002; Kim et al., 2011). In our country, it can be difficult to reach the gynecology specialists especially in the periphery and the lack of ultrasonographic examinations in primary health care services causes the diagnosis of the cases to be delayed and the risk of IMH increases. Therefore, in this article, the value of the tests in the diagnosis of MH including markers that can be examined in primary health care institutions was examined.

Materials and Methods:

Nineteen patients diagnosed as MH in the pathology laboratory of the tertiary health care institution between 2014-2017 were included in the study. Nineteen healthy pregnancies terminated on the day of registration of MH cases at the pathology laboratory were examined as control group. Hematoxylin & eosin stained preparations were from the pathology archive re-examined and histopathological diagnosis was confirmed.

In this retrospective study, biochemical and hematological test results were obtained from hospital information system. Blood tests were performed on the day of the intervention or on the previous day are used for analyses.

The analyses of glucose (fasting), uric acid, creatinine, C-reactive protein (CRP), sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH) prothrombin time (PT), international normalization rate (INR), clotting time (PTSN), activated partial thromboplastin time (APTT) and fibrinogen values between groups were performed with

Mann Whitney-U test in SPSS 15.0 package program. P values less than 0.05 were considered statistically significant.

Results:

The age range of the patients was 19-47 and the mean age was 33.8 ± 8.5. The age range of the MH cases was 19-46 and the mean age was 33.2 ± 7.3; and the age range of the control group was 19.5-47, mean age was 34.5±9.6. The mean values of biochemical analysis and thyroid function tests of the all cases, MH group and the control group and the p values obtained by Mann Whitney-U test between the MH group and the control group are given in Table 1.

	All cases (mean+ std)	MH group(mean+ std)	Control group (mean+ std)	p value
Glucose (fasting)	97.82±17.51	99.21±16.66	96.42±18.66	0. .483
Uric acid	3.61±0.82	3.45±0.72	3.77±0.89	0.334
Creatinine	0.70±0.47	0.62±0.17	0.77±0.64	0.639
CRP	0.64±1.25	0.44±0.25	0.83±1.75	0.704
Sodium	136.48±3.52	135.95±1.90	137.00±4.62	0.614
Potassium	3.97±0.72	3.82±.87	4.13±0.50	0.328
Calcium	9.33± 0.35	9.33±0.26	9.33±0.43	0.906
AST	19.61±7.54	21.26±9.55	17.95±4.47	0.463
ALT	20.26±14.25	21.26±19.21	19.26±6.81	0.320
Free T3	3.58±0.70	3.54±0.72	3.613± .70	0.872
Free T4	0.93±0.20	0. .89±0.17	0.96±0.22	0.301
TSH	1.62±0.97	1.64± .97	1.60±0.99	0.793

Table 1: *The means of biochemical examination results of all cases, MH cases and control cases and p values obtained by Mann Whitney-U test of MH and control groups*

As shown in Table 1, there are no statistically significant parameters between the MH group and the control group, and the averages are very similar when evaluated with standard deviations.

Mean values, standard deviations of coagulation-related markers of all cases, MH group and control group, and p values obtained by Mann Whitney-U test between MH and control groups are given in Table 2. As in the biochemical analysis, no statistical significance was observed in coagulation-related markers.

	All cases (mean+ std)	MH group (mean+ std)	Control group (mean+ std)	p value
PT	95.02±13.62	91.87±15.13	96.71±12.92	0.280
INR	1.01±0.17	1.04±0.22	0.99±0.083	0.598
PTSN	13.39±1.63	13.69±1.83	13.08±1.35	0.422
APTT	29.22±3.98	29.24±4.22	29.23±3.74	0.988
Fibrinogen	304.28±45.71	289.84±41.92	318.49±44.58	0.073

Table 2: *The means and standart deviations of prothrombin time (PT), international normalization rate (INR), coagulation time (PTSN), activated partial thromboplastin time (APTT) and fibrinogen values of all cases, MH group and control group, and p value of Mann Whitney-U test between MH and control group for these parameters.*

Discussion:

Gestational trophoblastic diseases are a group of diseases that show a wide spectrum of clinical, pathological features and genetic compositions. Mole hydatiform, which is one of the most benign diseases of the distribution, is the most common subgroup. Although beta hCG and ultrasonic examination play an important role in the diagnosis of MH, histopathologic examination is the most important method. In the diagnosis of MH, which is divided into two parts as complete and partial, histopathology for PMH is

sometimes insufficient. Molecular tests may be used in this situation and / or for karyotype evaluation of MH.

Myometrial invasion, independent of MH subtype, is called IMH. The most important conditions for MH are choriocarcinoma, development of GTN, IMH and recurrent MH. In the literature review, this trend was determined. It is noteworthy that most of the published studies are aimed at early recognition of IMH and persistent MH (Yang et al., 2002; Yang et al., 2002; Kim et al., 2011). Studies for early diagnosis and / or pre-histopathological diagnosis of MH can be roughly grouped as biochemical, hormonal and hemogram based evaluations.

Among the biochemical examinations, the blood values of 32 CHM and 30 healthy pregnant women were examined and it was reported that fasting sugar was found to be significantly higher in the CMH group compared to the control group (Verit and Hilali, 2011). In the present study, no significant statistical difference was observed between the mean fasting glucose values.

Pathological or normal trophoblasts produce HCG; and it is known that TSH and TSH receptors and HCG show analogy (de Almeida et al., 2011). For this reason, a list of symptoms -which is also known as thyroid storm- including hyperthermia, delirium, convulsion, tachyarrhythmia, high-output heart failure or cardiovascular collapse symptoms that may lead to even fatality has been reported (Kofinas et al., 2014; Moskovitz and Bond, 2009). Walkington et al. reported that the accompanying biochemical thyroid disease is relatively common in patients with GTH in the study that is conducted in United Kingdom UK by evaluating the 5-year period (Walkington et al., 2011). Approximately, hyperthyroidism occurs in 25–64% of MH cases (Garner et al., 2007; Palmer, 1994). In the present study, no cases of hyperthyroidism were found and there

was no statistically significant difference between the MH and control groups in terms of thyroid function tests.

When articles including hemogram and blood parameters were evaluated, it was reported that low natural killer cell percentage was associated with gestational trophoblastic tumors (Sutoto, 1999). n a study that included 257 MH and 198 normal pregnant women, mean platelet volume was reported to have an additive effect of 21.5% in predicting persistent MH (Abide Yayla et al., 2017). In a study published in 2019, the value of inflammatory cells in predicting MH was examined and it was stated that the ratio of lymphocyte means in healthy group was statistically significantly higher than MH group (Eroglu and Adali, 2019).

In studies involving coagulation parameters, coagulation and fibrinolysis tests were performed in 14 MH cases and 10 control cases, and it was reported that the most common anomaly was shortening of partial thromboplastin time and prolongation of thrombin time (López-Llera et al., 1977). Goldstein et al. reported that the changes in fibrinogen levels and plasma fibrinolytic system observed in GTH cases were similar to physiological changes seen in the 2nd and 3rd trimesters of normal pregnancy (López-Llera et al., 1977). However, the presence of MH cases with disseminated intravascular coagulation development (Henderson and Lund, 1971; Egley et al., 1975) indicated that coagulation and anticoagulation systems should be examined in detail in GTD. In the present study, parameters related to coagulation system were examined for the diagnosis of MH, but no statistical significance was found. Kaplan et al reported that they found shortened APTT in MH cases and that PTT did not change (Kaplan et al., 1985). They suggest that the fluids in HM have procoagulant activity and that the activation of blood clotting occurs at the X factor level (Kaplan et al.,

1985). They also suggest that placental and decidual focal necrosis seen in molar pregnancies, especially in CMH, may be associated with this situation (Kaplan et al., 1985).

Nowadays, early detection of pregnancies often leads to early detection of MH, but the findings of early MH are not pathognomic, making the diagnosis difficult. Furthermore, there is no definitive predictive test for post-molar trophoblastic disease. Moreover MH is a disease that can lead to fatality. In this study, which included biochemical, hormonal and coagulation analyzes, which were thought to be predictive for the MH, the parameters evaluated did not show statistical significance between the MH group and the control group, and even the mean values of the groups were close to each other. In this study, where the number of cases is limited, it is thought that the results of this study should be studied in larger case series in order to evaluate the relationship with this limitation. In addition, it is suggested that in a series including MH and IMH, the parameters studied in this study, especially the coagulation analysis, should be evaluated in terms of invasion predictivity.

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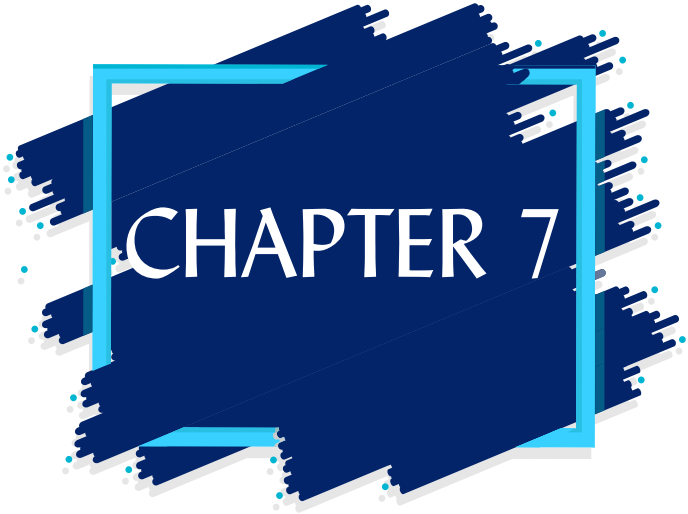
AN OVERVIEW OF ARSENIC TOXICITY WITH CURRENT LITERATURE

Hüseyin Avni EROĞLU



AN OVERVIEW OF ARSENIC TOXICITY WITH CURRENT LITERATURE

Hüseyin Avni EROĞLU

Arsenic is an tasteless, odorless element with the atomic number 33, which is frequently found in nature. Arsenic, which is accepted as the most important cause of environmental toxicity worldwide (Hughes et al., 2011; Goudarzi 2018), is generally found as arsenite (As2O3, As III) and arsenate (As2O5, As V) in 3 and 5-valent forms. Trivalent forms are known to be more toxic than other forms (Ratnaike, 2003; Hughes ve ark., 2011). Arsenic, referred to in history pages as "king of poisons" and "poison of kings" due to it's undetectable nature and until the middle of the 1850s it was used as the main tool of assassination (Hughes ve ark., 2011). Therapeutic use of arsenic is much older. In ancient Greek, arsenic, commonly used by scientists such as Hippocrates and Gallen which has begun to be used more commonly in the 19th century in the form of the "Fowler SolutionThis solution, which contains 1% potassium arsenite and is also called as health tonic, has been used as a treatment option in diseases such as leukemia, dermatitis, psoriasis, stomatitis and gingivitis in infants. This solution, which continued to be the main cure for these diseases until World War II, is currently used in the treatment of acute myeloid leukemia (Ratnaike, 2003). This treatment with arsenic trioxide primarily acts by regulating apoptosis regulation by increasing Bax expression, which is a member of the Bcl-2 family. Researchs on the use of arsenic trioxide as a treatment option for other types of neoplasias are continuing due to its success in the treatment of this disease. (Sekeres, 2007; Hughes ve ark., 2011).

It is possible to see that arsenic is spread over a wide range of application fields. It is used in cosmetic products, as pesticides to protect agricultural products, as pigment in

dyes (especially Paris green) and in industry. It is widely used in mining and foundry works in industry. Arsenic toxicity is frequently seen with exposure in all of these areas of use. And naturally arsenic exposure is a problem for those working in these areas. However, the biggest problem is the toxicity of arsenic, which reaches to a wider mass through its mixing as a result of its use as a pesticide. Prolonged exposure of arsenic to drinking water can cause serious health problems due to its carcinogenic properties as well as toxic effects on many organ systems (Ratnaike, 2003; Hughes ve ark., 2011). In many countries, including Bangladesh, Chile, China, India, Mexico, the United States and Brazil, arsenic toxicities from drinking water have been reported (Souza ve ark 2016). According to the World Health Organization, the maximum acceptable exposure was 50 µg / L, and after 1993, 10 µg / L was standardized as an acceptable limit. (Ratnaike, 2003; Hughes ve ark., 2011). However, from time to time, the limits that countries set for themselves change. For example while 10 µg / L limit is still used in the USA, it is accepted as 5µg / L upper limit in Canada. (Kapaj ve ark., 2006).

Arsenic taken into the body through drinking water, food and skin is and it is absorbed through the small intestine through the electron gradient. Arsenic is converted to less harmful monomethylarsenic acid (MMA) and dimethylarsenic acid (DMA) in the liver by methylation. Approximately 50% of the methylated amount is removed from the body through the urinary system in 3-5 days. But a small amount of arsenic cannot be methylated and accumulates in organs. While arsenic accumulates in the kidneys and liver in acute toxicity, it is mainly observed in the liver, kidneys, heart and lungs; and observed in small amounts in muscle tissue, gastrointestinal system and spleen. About two weeks after exposure, arsenic begin to accumulate in keratine-rich tissues like hair and nails (Ratnaike, 2003; Hughes ve ark., 2011).

Acute arsenic toxicity occurs by exposure to high doses of arsenic at one time. In acute arsenic poisoning, the lethal dose is 100-300 mg. Nowadays, acute toxicity is usually seen by accidental ingestion of pesticides and inhalation of arsenic gas in occupational work environments, but to a lesser extent in suicide and murder. Clinical symptoms include diarrhea, vomiting, pain, dehydration, and weight loss. Neurological symptoms such as delirium, encephalopathy and peripheral neuropathies may also be included in the clinical presentation. In addition, hematological changes such as hemaglobinuria, bone marrow depression, anemia and basophilic stipling, renal failure, respiratory failure and pulmonary edema are also common. (Ratnaike 2003; Vahidnia 2007).

Chronic arsenic toxicity occurs through low concentration and prolonged exposure to arsenic: in other words “arsenicosis”. Chronic toxicity is a common and serious health problem (Kapaj ve ark., 2006; Vahidnia ve ark., 2007). Generally, exposure occurs through drinking water or in arsenic-treated environments. Common symptoms are hyperpigmentation, hyperkeratosis on palmo-plantar faces of hands and feet and Mee lines on nails. (Ratnaike, 2003; Paul ve Giri, 2015). However, chronic exposure may also cause diabetes, hypertension, gastrointestinal disorders, neurological disorders, cardiovascular and/ or kidney diseases. (Huang ve ark., 2017). According to a study by Zierold et al. (2003) even exposure to arsenic with a concentration of less than 2µg / L can cause , high blood pressure and circulatory problems in cardiac bypass surgery. (Zierold ve ark., 2003). Arsenic, which increases reactive oxygen derivatives (ROS), causes DNA damage due to increased oxidative stress. As a result, people exposed to arsenic may develop many diseases, including cancer types (Paul ve Giri, 2015).

One of the target organs of arsenic is liver, the organ where metabolization and detoxification takes place. Diseases such as hepatomegaly, hepatic fibrosis, portal hypertension and liver tumors have been reported in arsenic toxicity (Sankar ve ark., 2015). These diseases are caused by hepatocyte degeneration, inflammation, necrosis and apoptosis in the liver (Bali ve ark., 2016). Studies have shown that arsenic exposure changes enzyme activities in the liver, increases lipid peroxidation, reduces glutathione (GSH) and reduces the activity of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) (Li ve ark., 2015).

Another organ affected by arsenic toxicity is the brain. Arsenic, which passes the blood-brain barrier, tends to accumulate in brain tissue (Prakash ve ark., 2016; Goudarzi ve ark., 2018). Although the mechanism of arsenic neurotoxicity is not fully explained, mitochondrial dysfunction, increased lipid peroxidation, induced apoptosis, increased calpain content, thiamine deprivation and decreased acetylcholine count can be counted (Mochizuki, 2019). Clinically, toxicity causes neurobehavioral disorders, including symmetrical peripheral neuropathy, paralysis, confusion and delirium (Prakash ve ark., 2016; Goudarzi ve ark., 2018). In human and animal studies that are conducted, it was determined that arsenic toxicity affects spatial learning and memory (Soni ve ark., 2017). Yadav et al. (2010) showed that even low levels of arsenic exposure reduced dopamine, norepinephrine, seratonin levels in the brain, and this decreased neurotransmitter levels lead to decreased cognition in rats (Yadav ve ark., 2010; Prakash ve ark., 2016). Lou et al. (2019) confirmed the correlation between morphological and chemical changes in the hippocampus and spatial learning in rats exposed to arsenic from drinking water (Lou ve ark., 2019).

When the effect of arsenic on reproductive system is examined, histopathological changes in male reproductive system are seen in testes. Changes in the antioxidant enzymes in the testis, differences in the weight of the reproductive organs, changes in testosterone level and decrease in sperm function and number is reported (Souza ve ark., 2016). Huang et al. (2016) showed that fertility is difficult due to low testosterone level, abnormal testicular spermatogenesis and obstacles to sperm attachment to oocytes in rats exposed to arsenic (Huang ve ark., 2016). Wang et al. (2006) found a positive correlation between even low level of environmental arsenic exposure and male reproductive system infertility (Wang ve ark., 2006). In addition, epidemiological studies suggest that arsenic exposure reduces human semen quality and increases the risk of prostate cancer (Huang ve ark., 2016). Arsenic also has effects on the female reproductive system and fetus. Studies have found significant correlations between arsenic toxicity and deterioration of fetus development, and the toxic effect has been shown to cause premature labor and abortion. In rats, it has been revealed that it suppresses ovarian steroidogenesis, prolongs estrogen release and also causes degeneration in ovarian follicle and uterus cells (Kapaj ve ark., 2006).

Arsenic exposure has long been proven to increase cancer risk, and in 1922, arsenic was first used by Leitch and Kennaway in carcinogenic animal modeling. The International Agency for Research on Cancer (IARC) clearly demonstrates the relationship between arsenic exposure and skin, lung and gallbladder, while its knowledge of its relationship with liver, kidney and prostate cancer remains limited (Zhao ve Xi, 2018). Skin cancer is the most common form of malignancy and lung cancer is the most lethal form of cancer in arsenic exposure. When the internal organs are examined, the gallbladder is the organ with the highest carcinogenic risk (Sinha, 2013).

Recent investigations have shown positive relationships between cancer areas in humans and geographic areas with high arsenic concentrations in drinking water. In particular, exposures above 50 µg / L significantly increase the statistical difference (Malats ve Real 2015).

There is still no definitive treatment for chronic arsenic toxicity, which is a disease affecting many other systems as well as the systems mentioned in detail above. However, chelation therapy, new generation chelation therapy and antioxidant therapy are the treatment methods used against this toxicity. The main purpose of chelation is to remove arsenic from systems and the body with the help of another ligand. The selected chelating agents should therefore be non-toxic, water-soluble, high affinity to arsenic, and readily removable from the body. The first agent made for this purpose was 2,3-dimercapto-1-propanol, which was developed by Lewis and called anti British anti-Lewisite (BAL). D-penicillinamine was developed after BAL because it releases arsenic in the brain, causes nephrotoxicity, hypertension and tachycardia.. The disadvantages of D-penicillamine have led to the development of a third chalcation agent, meso-2,3-dimercaptosuccinic acid (DMSA). While DMSA is advantageous in terms of low toxicity and preventing the spread of arsenic to other organs, it is insufficient in the salivation of intracellular components as it does not pass through the cell membrane. It also causes gastrointestinal problems, neutropenia, elevated liver enzymes and skin allergies. 3-dimercaptopropane-1-sulfonic acid (DMPS) is a water-soluble chalcionate derived from DMSA and has a lower side-effect profile. Monoamyl DMSA (MiDMSA) and monocyclohexyl (MmDMSA) are also other chalcation agents derived from DMSA. Due to the insufficiency of the old ones, the new generation of the new generation of therapies was developed. DMSA and MiDMSA, quercertin with DMSA, DMSA with N-acetyl

cysteine, alpha lipoic acid and DMSA are two agents combined. Finally, antioxidant treatment methods are the preferred method for arsenic toxicity. Reducing the increase in ROS caused by arsenic is the main strategy and various agents and treatment methods are used for this purpose (Kosnett, 2013; Susan ve ark., 2019).

As a result, it is important to understand the mechanism and clarify its effects on organs and systems while arsenic toxicity is becoming a more common problem with increasing environmental pollution -especially chronic arsenic toxication-. Therefore, there is a need to develop more effective treatment methods. For this purpose, studies should be increased and improved.

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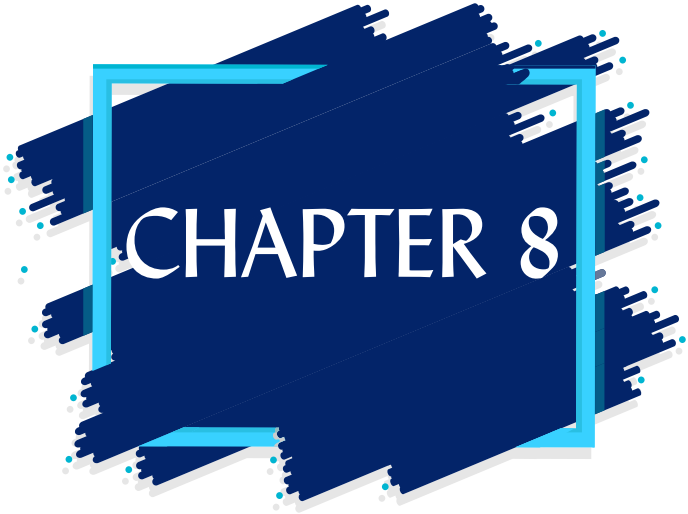
THE EFFECT OF JOB STRESS ON BURNOUT IN HEALTHCARE PROFESSIONALS

Hüseyin ERİŞ[1], Sinem BARUT[2], Osman ÖZKAN[3]



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1. INTRODUCTION

The concepts of stress and burnout are the leading ones among subjects mostly addressed by recent studies. The concepts of stress and burnout can be defined as the disease of modern life and they are thought to affect each other. Numerous studies have been conducted on stress and burnout in different disciplines such as medicine, organizational psychology, management science, and engineering and different definitions have been suggested for these concepts in the literature. Therefore, stress and burnout develop in different forms in individuals and organizations and affect negatively the individual, the organization and the community at certain levels.

Relationships between work and stress have led researchers to conduct studies on job stress. For example, it has been suggested that some professions such as manager, police, soldier, and nurse in the service sector have the highest stress levels (1, 2). There are numerous studies that scientifically address and examine the level, sources, solutions, and coping methods of job stress. The previous studies suggest that many potential stressors such as occupational identities, role overload, tension associated with interpersonal relations, career prospect, workplace problems, insufficient resources, lack of institutional support, and role conflicts as well as the stress caused by private lives of the employees threaten the health of employees (3).

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Today, most of health institutions operating in the service sector are trying to maintain organizational and physical development; on the other hand, they can ignore the conditions of healthcare professionals such as working conditions, job stress, burnout, and motivation. However, since the negative situations experienced by healthcare professionals in the health institution reflect negatively on their performance, they also reflect negatively on performance of the health institution. Especially due to the problems in the health services in Turkey (health policies, excessive number of patients, inadequate and unqualified health personnel, lack of physical space and equipment etc.), particularly healthcare professionals face with many problems. These problems can lead healthcare professionals to experience burnout and have an increased job stress by making their working conditions hard. Especially doctors and nurses in the health institutions suffer from job stress and burnout at higher rates because of misconducts displayed by patients and their relatives (4).

2. JOB STRESS

Stress is defined as an applied force or power system that deforms or shows the tendency of deforming an object (5). Hans Selye was the first person to study the subject of stress . According to definition of stress by Hans Selye, regarded as the modern day father of stress, in 1936; stress is "the non-specific response given by the body to any change demand". Hans Seyle expanded his stress definition in 1979 by stating that "stress is a 'perception'. It is the demands imposed upon us due to the presence of too many alternatives" (6). Stress has been considered as an occupational hazard since the mid-1950s. (7). There are different definitions of stress made by authors in the literature. Stress can be defined as emotional and physical reaction towards stressors (8, 9). Stress can also

be stated as experiencing the emotions which have various effects on others and cause anxiety, sadness, tension, and pressure (10). Stress can also be defined as physical and chemical reactions given by an organism depending on some stressors (11). Physiological, psychological, and behavioral effects of the stressor on individuals have been extensively suggested by the recent studies (12, 13,14).

Stress can develop due to external reasons or individuals' psychological state (15). It is also seen that stressors causing stress in human life can be both material and immaterial-based and extreme stress leads to some physical and psychological problems in individuals (16).

Work has an important place in human life. The relationship between work and stress has led scholars, who study in different fields, to conduct studies on job stress. While job stress has a significant effect on the personnel today, the importance of job stress for both institution and the personnel has been also supported by many studies (17, 18). Job stress is defined as a condition arising from physical or psychological reasons and also the individual's incompetence and causing tension in the individual (19, 20, 21, 22). As a matter of fact, occupational stress has been regarded as an important health issue. (7) Job stress is the reaction that does not meet the knowledge and skills of individuals and compels their coping skills when they encounter with the work demands and pressures (23).

It is also determined in studies that the negative factors related to the workplace result in physiological and psychological pressures and destructions on employees and affect negatively their health and successes (24, 25). In particular, increasing the labor turnover, absenteeism, desire to leave the work and burnout can be regarded among the most important outcomes of stress (24). The studies on job stress have revealed some negative effects

on the personnel and institutions. It is shown that the job stress causes problems such as decreased motivation and job satisfaction, alienation to work, low productivity, and absenteeism among the personnel. The possibility of being unhealthy, less motivated, less productive and less secure at workplace increases for an individual working in a stressful environment (24, 26). It was determined as a result of the studies that many potential stressors such as occupational identities, role overload, tension associated with interpersonal relations, career prospect, workplace problems, inadequate resource and institutional contribution, and role conflicts as well as stress caused by the private lives of the working individuals threatened their health (12, 3). The studies showed that job stress imposes high cost in human and financial aspects (27).

Many recent studies have addressed job stress among healthcare professionals. As healthcare professionals face various psychosocial stressors, they have a high risk of developing burnout syndrome, which in turn can influence hospital outcomes like the quality and safety of care (28). Researchers have evaluated job stress among medical technicians, radiation therapists, social workers, occupational therapists, physicians and collections of healthcare staff throughout disciplines (7). Tel et al., (2003) determined the causes of job stress in health institutions as healthcare approaches and new practices and expectations arising as a result of the organizational changes, work environment, excessive workload, interpersonal problems, and working with patients who require intensive care or are about to die (29). In addition to the difficulty of providing service to the patients and their relatives in the health sector, hardworking health professional experiencing intense stress are separated from other occupational groups due to the fact that they constantly face with stress in the hospital environment. The reasons such as inadequacies in health service and unbalanced distribution of service and

personnel as well as long working hours, heavy workload, providing care to the patients with seriously ill who have severe diseases, and death of patients cause disappointment and tension in healthcare personnel (29, 30, 31).

2.1. Burnout

Burnout is a very serious feature of chronic stress that can impair the effectiveness of human service worker (32). The concept of burnout, which is an important issue for both personnel and institutions, has gained an important place in the literature in recent years and has started to be common especially among the personnel working in the service sector (33). The concept of "burnout" was introduced by Freudenburg in 1974 in the literature for the first time (34). Although the concept of burnout has many different definitions in the literature, the accepted definition in the literature was made by Maslach in 1981. Maslach defined the burnout as a syndrome that is associated with the development of helplessness, loss of respect, chronic fatigue and feelings of despair that cause negativities on the personnel when they are exposed to intense emotional demands in the work life and the relationships with other people and concerns physical, emotional, and conscious exhaustion experienced against work, life, and other people (35).

While Freduenberger (1974) defines only the emotional exhaustion dimension of the burnout (36), Maslach divides the burnout into three subcategories as emotional exhaustion, depersonalization, and personal accomplishment (11). Maslach defines burnout as a syndrome commonly seen in individuals working in the service sector as (a) "feeling exhausted in emotional way", (b) "their depersonalization against other people as the nature of their work", and (c) "decrease in the personal accomplishment/competence feelings" (37). When the

definition of Maslach is examined in details, it is seen that burnout has numerous negative effects on personnel (38). In the light of this information, it can be asserted that burnout syndrome develops with the decreased personal accomplishment as a result of the increased emotional exhaustion and depersonalization levels in individuals.

It is known that burnout has two main reasons as environmental and individual (39). The quality of work, overtime hours, lack of organizational support, work load, and the characteristics of the persons served can be given as examples for environmental reasons. The characteristics such as age, gender, education, personal expectations, ego, and motivation can be given as examples for individual reasons.

Being defined as one's partial or complete disruption of the work and inability to really deal with people receiving service or not devoting himself/herself sufficiently to the work as a response to extreme stress; burnout syndrome is seen mostly in people working in service sector and in professions where the element of human has a very important place in the quality of service. Individual suffering from burnout syndrome affects the service and the quality of service negatively. The studies have shown that burnout has a wide range of serious consequences ranging from work loss to intra-family relationship problems, from psychosomatic diseases to alcohol-substance-cigarette use, and even mental illnesses such as insomnia, depression (40).

2.2. The Relationship between Job Stress and Burnout

The concepts of stress and burnout are actually different concepts although they are used interchangeably for each other in daily life. While stress is defined as the physical

and chemical reactions of individual depending on some distressing factors (23) burnout is defined as a professional person' getting off the original meaning and purpose of his/her profession and being unable to really deal with the people receiving service (41). The job stress described as a response in the cases where knowledge and ability of the personnel is inadequate against the work demand and pressure and they fail to use coping methods is different than multidimensional burnout (23).

Maslach who conducted the leading studies in this subject stated that long term job stress (chronic cases) causes burnout in employees (1, 41, 42). Concerning the relationship between job stress and burnout, Felton (1998) reports that burnout is seen as finished physical or emotional power of individual as a result of long-term stress (43). Cotton (1990) sees burnout as the result of failure to cope effectively with stress (44). In the definition made by Maslach, Leiter and Schaufeli (2008) to determine the association between job stress and burnout, they state that burnout is a psychological syndrome developing as a response to chronic stress factors at work (45). In other words, when the stress level of the individuals increases and they are not able to cope with this stress level, burnout syndrome develops.

Burnout is considered as an advanced and chronic state of stress. This situation was defined by Kaçmaz as 4 stages (40). The first stage is the desire and enthusiasm. At this stage, the individual exhibits a high level of happiness, increased energy, and unrealistic professional expectations. At second stage, there is a decrease in the will and happiness of the individuals. They start to feel disturbed by the difficulties they face while performing their profession as well as some points they had never cared or had denied before. In other words, at this stage the individuals have begun to notice some problems and

imbalances in the institution they work in. At the third stage, the individual understands how difficult it is to change people, system, negative working conditions, and starts to feel being hindered. The final stage is the burnout state in which stress cannot be coped with and the exhaustion is felt. In other words, very deep emotional collapse, a deep disbelief and despair are observed in individuals. They keep their job for an economic income and do not enjoy their work.

As a result, work-related stress is one of the most common health issues of employees (46). Burnout syndrome which develops due to chronic stress and is unpreventable (1) causes mental problems in individual such as depression, anxiety, and feelings of helplessness as well as physiological problems such as headache, muscle tension, and insomnia (1, 41, 42). It also results in negative organizational consequences such as work-related tension, reduced productivity and production at work, reduced job satisfaction, delayed work, absenteeism with alleged excuses or leaving the work and thus not keeping the experienced personnel (47). In addition, a higher probability of exhaustion is observed in the hospitals which have a complicated structure and in turn role conflicts or uncertainties (2).

3. MATERIAL AND METHOD

Purpose of the Study: The purpose of this study was to determine the effect of the job stress on burnout among healthcare professionals.

Population and Sample: The study was conducted on approximately 4.000 staff members working in a state hospital, a university hospital, and a private hospital located in the city center of Şanlıurfa. When confidence interval and level were calculated as 0.5 and 95% using

simple random method, the sample size of the study was calculated as 351. In the study, Job Stress Survey developed by Vagg and Spielberger and the Maslach Burnout Inventory were applied between 15.06.2018 and 30.09.2018. 458 hospital employees participated in the study. Before conducting the study, ethics committee approval from Harran University Ethics Committee and written permissions from the Şanlıurfa Secretariat General of Public Hospitals, to which the mentioned district public hospitals are affiliated, were obtained.

Table 1 shows the distribution and percentages of the healthcare professionals in terms of the district hospitals they worked in.

Table 1. *Distribution of the Healthcare Professionals in terms of the Hospitals*

Hospital	Number	Percentage
Harran University Research and Application Hospital	171	37.4
Şanlıurfa Training and Research Hospital	210	45.8
Private Hospital	77	16.8
Total	458	100.0

When examining Table 1, it was seen that 37.4% of the healthcare professionals were working in Harran University Research hospital, 45.8% were working in Şanlıurfa Training and Research Hospital, 16.8% were working in the private hospital.

Data Collection Tool: This cross-sectional study consisted of three sections. In the first section, there were questions prepared by the researchers to determine the demographic and occupational characteristics of the healthcare professionals. In the second section, the Maslach Burnout Inventory was used. In the third section,

the Job Stress Survey (JSS) developed by Vagg and Spielberger (1999) was used. Each item in the survey was rated in a 5-point likert scale as; “Never (1)”, “Seldomly (2)”, “Sometimes (3)”, “Usually (4)”, and “Always. (5)”

For the data collected by using the questionnaires in the study, a database was formed and data were input by using SPSS 11.5 statistical packaged software. Firstly, the reliability studies of two scales used in the study and the descriptive statistics were conducted. While the construct validity of the scales used in the study was investigated with CFA model, the effect of the job stress on burnout was examined with SEM model. In the study, the effect of the job stress survey on burnout was also examined.

3.1. The Reliability of the Study

High alpha coefficients of the related scale is interpreted as the fact that “the items in this scale are consistent and the scale consists of the items checking the elements of the same property or all items function together in that measure. İt was determined that while the Cronbach’s alpha coefficient of the job pressure subscale of the job stress survey used in the study was .882, the Cronbach’s alpha coefficient of the Lack Of Organizational Support subscale was .885. The Cronbach’s alpha coefficient was calculated as 0.875 for the emotional exhaustion subscale, 0.836 for the depersonalization subscale, and 0.779 for the personal accomplishment subscale in the burnout inventory. When examining these values, it can be asserted that the reliability values of the scales used in this study were high.

Table 2 shows the demographic characteristics of the healthcare professionals participating in the study.

Table 2. *The Socio-demographic Characteristics of the Healthcare Professionals*

Age groups	N	%
27 years and below	252	55,1
28-32 years	206	44,9
Gender		
Female	221	48.2
Male	237	51.8
Marital Status		
Married	163	35.5
Single	275	60.5
Divorced	21	4.0
Educational Status		
High school	76	16.3
Associate's degree	76	21.0
Bachelor's degree	210	46.2
Medicine – Med. spe.	76	16.5
Profession	N	%
Physician	78	16.5
Nurse - midwife	262	57.6
Health technician	119	25.9
The working period at profession		
1 or 3 years	241	52,6
4 years and more	217	47,4
The working period in the region		
1 or 2 years	278	60,7
3 years and more	180	39,3
Total	458	

According to the results obtained in Table 2, 55.1% of the healthcare professionals participating in the study were in the age group of 27 and younger, 51.8% were female, 60.5% were single, 46.2% had a bachelor's degree in terms of education, 57.6% were nurse/midwife in terms of

profession, 52.6% were in the group of 1-3 years in terms of professional experience, and 60.7% were involved in the group of 1-2 years in terms of working in the region.

Table 3. *Statistical Values of Goodness of Fit for Validity of the Model*

	Job Stress Survey CFA	Burnout Inventory CFA	SEM
CMIN/ DF	3.175	2.956	2.757
GFI	0.091	0.901	0.807
CFI	0.930	0.916	0.851
RMSEA	0.070	0.066	0.063

While the construct validity of the scales used in the study was examined by using the Confirmatory Factor Analysis model, the effect of job stress on burnout was investigated by using the Structural Equation Model. Table 3 shows the statistical values of goodness of fit of the models. According to the obtained results, it was observed that while Confirmatory Factor Analysis models met necessary requirements for CMIN/DF, GFI, CFI and RMSEA criteria, the Structural Equation Model met necessary requirements for CMIN/DF and RMSEA criteria.

Table 4 shows the data obtained concerning the effects of the job stress and its subscales on burnout were examined.

Table 4. *The Effects of the Job Stress and its subscales on Burnout*

	Direct effect		Indirect effect	
	Estimation	S. Estimation	Estimation	S. Estimation
Job Stress (Overall Scale)	1	0.667	0	0
Lack of Organizational Support	0	0	0.730	0.665
Job Pressure	0	0	1	0.666

Table 4 shows the effects of job stress and its subscales on burnout. All effects were found to be statistically significant according to the model. The results revealed that the effect of the job stress on burnout was 0.667. The effects of the subscales of the job stress on burnout were calculated as 0.665 and 0.666. These close values were associated with the fact that the job stress subscales had a high correlation between each other and they had similar effects on the scale.

3.2. Discussion

In this study, the effect of the job stress experienced by the healthcare professionals due to the intense and hard working conditions on their burnout was determined. The relationships between job stress and burnout were not examined in terms of socio-demographic characteristics. The results obtained in the study pointed out that the job stress had an effect of 0.667 on burnout. In other words, a one-unit increase in job stress levels of healthcare professionals would have an effect of 0.677 units on their burnout levels; in other words, it would increase the burnout level of the healthcare professionals. It was observed that the job stress had a significantly high effect on burnout.

When the studies on determination of the relationship between job stress and burnout in the literature were examined, it was found that the increased job stress level caused an increase in the burnout level (25, 28, 31, 48, 49, 50, 51, 52). The results of some studies in the literature showed similarities with the results of the present study. For example, in the study entitled “Job stress and burnout in hospital employees” conducted by Chou, Li and Hu, in a regional hospital in Taiwan in 2014, they stated that the job stress affected the burnout and the mostly affected occupational group was resident physicians.

In another study entitled "Burnout and Job Stress among Mongolian Doctors and Nurses" conducted by Bagaajav et al., in 2011, they reported that doctors and nurses felt distress and were at a high risk due to the burnout associated with job stress. In the study, it was also determined as a result of the regression analysis between job stress and burnout that job stress significantly affected the feeling of burnout significantly in all aspects. In their study, Bennett, Plint and Clifford (2005) pointed out the relationship between burnout and high level of job stress and determined that the burnout was more common among non-physician healthcare professionals.

As a result of a study conducted by Zhang et al., (2014) on 9.698 nurses working in 181 hospitals in China, they determined that the nurses were experiencing high level of burnout due to stress caused by poor working conditions (53). In the study entitled "Burnout in Healthcare Professionals in Oncology" conducted by Font, Corti, and Berger (2015), it was found that majority of the healthcare professionals working in the oncology service had burnout symptoms and this was usually associated with emotional relationships with the patients as well as excessive workload, managerial problems, and the communication problems among the personnel (54).

In the study conducted by Ardıç and Polatçı in 2007 with the academicians, they found that 200 academicians were experienced a high feeling of burnout due to various stresses factors. In this study, it was emphasized that individuals working in the same profession and the same institution would experience different levels of burnout due to their different characteristics. It was also found that the burnout levels of the academic personnel varied based on their various socio-demographic characteristics in emotional exhaustion, depersonalization, and personal accomplishment subscales of the Maslach burnout inventory (55).

3.3. Conclusion and Recommendations

This study was conducted to determine whether or not job stress had a direct effect on burnout. As a result of the study, it was determined that an increase in the job stress level of healthcare professionals had a high effect on their burnout level. As the stress level increased, the burnout level also increased. Similar results have been determined in many studies conducted in both health sector and other sectors. In other words, the job stress is seen to have a high significant effect on burnout.

Each occupational group experiences a certain level of stress due to a number of stress factors. In addition, professions especially in the service group are more stressful than the others. In the service sector where the human effort has a very important place, stress-related burnout causes enterprises to suffer economic losses and have serious problems, personnel to leave the job early, and quality of the service to impair. Job stress and burnout have not only individual aspect but also institutional and social dimensions. Job stress and burnout syndrome experienced by the personnel working in the health institutions affect negatively the quality of healthcare service provided to the patient and the health, work performance and job satisfaction of the personnel receiving the service.

By setting high goals in the work life, job stress can be seen to be higher in individuals having big expectations. While excessive ambition, passion, and desire push the individual into a more stressful work life, the individuals who have not reached their goals are affected by stress more and they begin to experience chronic stress. Individuals who know how to cope with stress can experience a low level of stress and get rid of this process in a short period of time. In addition, the characteristics of the individuals, the harmony of their personality structure to the structure

of their work, and their awareness on possible problems in the work life may help the individuals to experience less or no burnout by being exposed to less job stress.

In the light of these data, there are some measures required to be taken by both the health personnel and managers in the health institutions in order to prevent or eliminate the feeling of burnout by reducing or eliminating the job stress. These managerial and individual measures can be briefly summarized as follows.

Actions to be taken at managerial level in the health institutions:

- Managers can protect the personnel from the stress associated with workplace
- Reducing long working hours of healthcare professionals,
- Organizing social activities inside and outside the hospital for healthcare professionals,
- Providing qualified personnel by eliminating the insufficient number of healthcare personnel,
- Holding meetings in the hospital, determining the problems of the personnel, and eliminating these problems,
- Having knowledge about the job stress and burnout issues,
- When healthcare professionals feel uncomfortable in situations such as job stress and burnout, it will be beneficial for them to share this with the management and to apply a specialist psychologist or psychiatrist for professional support.

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THE HEALING EFFECTS OF APRICOTS IN ACETAMINOPHEN-INDUCED LUNG DAMAGE

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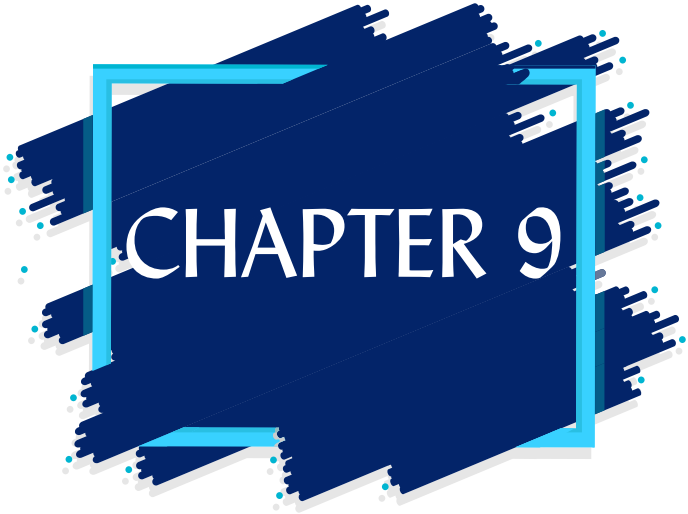

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THE HEALING EFFECTS OF APRICOTS IN ACETAMINOPHEN-INDUCED LUNG DAMAGE

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INTRODUCTION:

Acetaminophen is also known as N-Acetyl-p-Aminophenol (APAP), or paracetamol. It has strong analgesic and antipyretic effects and a weak anti-inflammatory effect, which is the result of the fact that it selectively decreases the production of cyclooxygenase (PGE2 in particular) in the central and peripheral nervous systems(Lucas, Warner et al. 2005). Therapeutic level: 10-30μg/ml. The recommended dose is 650 mg every 4-6 hours (4 g/day) for adults and 10-15 mg/kg every 4-6 hours for children. Although the treatment dose is safe, in excess doses, APAP causes severe liver failure through its toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). (Nassini, Materazzi et al. 2010) However, previous epidemiological studies associated the use of APAP in its previous therapeutic doses with chronic obstructive pulmonary disease (COAH) {Nassini, 2010 #24}. Plack et al. observed changes in four tissues in addition to the liver, i.e., kidney,lung, testicle, and lymphoid tissues, in mice that were administered 600 mg/kg acetaminophen. They found that the onset of these extrahepatic lesions, except for kidney damage, was delayed compared to liver damage. The common feature of liver and kidney toxicity is that both organs are the target tissues that metabolize the enzymes involved in the production of the last reactive metabolites that are the mediators of toxicity(Placke, Wyand et al. 1987).

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However, epidemiological studies conducted in the last decade have demonstrated that even intrauterine exposure to APAP (in therapeutic doses) poses a risk of asthma(Eneli, Sadri et al. 2005) (Allmers, Skudlik et al. 2009) and COPD (McKeever, Lewis et al. 2005) during infancy(Shaheen, Newson et al. 2002), childhood(Del-Rio-Navarro, Luna-Pech et al. 2007), and adulthood(Shaheen, Sterne et al. 2000)(Barr, Wentowski et al. 2004).

The apricot is a stone fruit, which is grown extensively in Malatya, a province located in Eastern Turkey.(Akinci and Olmez 2004) The apricot (Prunus armeniaca L.) contains high levels of carotenoids, mainly beta carotene, which is a source of provitamin A (Ruiz, Egea et al. 2005) . It also contains vitamin C, vitamin E and selenium (Se) (Munzuroglu, Karatas et al. 2003). The results of previous studies have demonstrated that beta carotene has free radical scavenging and singlet oxygen quenching effects which indicate the hepatoprotective benefits of carotene against acetaminophen(Manda and Bhatia 2003).

This present study aims to observe the potential damage to lung tissue caused by the most common APAP used as antipyretic and analgesic and to investigate the healing effects of apricots, which is rich in beta carotene.

2. Materials and Methods:

2.1. Animals:

The study protocol was approved by the Ethics Committee of İnönü University by decision number 2013/ A-72. 24 female Sprague-Dawley rats with an average weight of 194±20 g were used in the experiment. The animals were supplied by the experimental animal research and reproduction center at İnönü University, and the Rules of Care and Use of Laboratory Animals were applied.

2.2. Experimental design

The rats were randomized into four groups consisting of an equal number of animals (n=6). Group 1: Control, Group 2: Acetaminophen (APAP) (835mg/kg single dose, oral route), Group 3: APAP (835mg/kg single dose, oral route) + Apricots (10%), Group 4: Apricots (10%). All rats were fed normal rat feed and tap water without restriction. Standard rat feed (Elazığ, Turkey) and the Kabaaşı species of apricot supplied from a local market in Malatya (certified organic) were used in the study. 9 kg of pelleted rat feed and 1 kg of apricots (10%) were homogenously mixed by hand in a clean container. The mixture was dampened by a simple device for 5-6 days at room temperature, and given to the rats in pellets.

2.3. Histopathological procedures

The rats were sacrificed on the 45th day under ketamine/xylazine anesthesia. The lung tissue collected for examination under the light microscope were fixed in a 10% formalin solution. The tissue collected was subjected to routine histological tissue follow-up procedures and embedded in paraffin blocks. The sections of 5µ thickness were stained with a hematoxylin eosin (HE) stain. The sections were evaluated under a Leica DFC280 light microscope by Leica Q Win Image Analysis System (Leica Micros Imaging Solutions Ltd.; Cambridge, U.K).

Statistical Analysis: The statistical differences between the groups of parameters was evaluated by the Kruskal-Wallis test. The Bonferroni correction of the MannWhitney U test was used for multiple comparisons. The data was summarized as median values (min-max), and $p < 0.05$ was considered statistically significant.

Results: In the control and 10% apricot groups, the structure of the bronchi, bronchioles and the alveoli

were observed to have a normal appearance (Figure 1,2). APAP generally disrupted the alveolar structure in the lungs. In this group, mononuclear cell infiltration in the periphery and parenchyma of the alveolar vessels (Figure 3,4), thickening of the alveolar wall (Figure 5), alveolar expansion (Figure 9), vascular congestion (Figure 3,6), hemorrhage (Figure 7), necrosis, and perivascular fibrosis were observed upon detailed examination. A distinct reduction was detected in the histopathological findings in the APAP + 10% Apricot group (Figure10,11,12).

Discussion:

Paracetamol poisoning is the most common cause of fulminant hepatic failure {Bray, 1993 #22}. Severe cases rapidly progress to multi-systemic failure through the peripheral circulation and changes in the brain and kidneys {Baudouin, 1995 #23}. However, epidemiological studies have demonstrated that APAP may potentially pose asthma and chronic obstructive pulmonary disease (COAH) risks even in therapeutic doses {Allmers, 2009 #25}. Hence, this study investigated the acute damage caused by high-dose APAP on the lungs, which is one of the extrahepatic tissues. The mononuclear cell infiltration in the peribronchial and perivascular region was evaluated as inflammation. Nassini R. et al. also observed neurogenic inflammatory responses due to TRPA1 in the airways when they administered therapeutic doses of APAP (including doses recommended for children) to rats {Nassini, 2010 #24}. Necrosis of the bronchial epithelium following oral administration of acetaminophen is consistent with cases of pulmonary injury that have developed as a result of agents entering the body by means other than inhalation {Placke, 1987 #21}. In addition, as most epithelial tissues contain enzymes needed to produce toxic metabolites of acetaminophen, acetaminophen toxicity which is already

extrahepatic cannot be completely ruled out {McKeever, 2005 #29}.

Glutathione, an endogenous antioxidant, exists in the airway epithelia in high concentrations {Cantin, 1987 #26} and evidence suggests that decreased glutathione levels are associated with oxidant damage in the lung {Jenkinson, 1988 #27}. Furthermore, glutathione is implicated in drug detoxification, particularly in the metabolism of acetaminophen. Animal studies have demonstrated that acetaminophen in high doses decreases glutathione levels in lung tissue {Micheli, 1994 #28}. Therefore, regular acetaminophen users may be at risk of lung tissue damage, and ultimately, respiratory tract diseases due to the depletion of glutathione.

The health enhancing properties of fruit and vegetables result from their high vitamin, phytochemical and fiber content. Apricots are a fruit rich in phytochemicals and vitamins {de Kok, 2008 #30}. However, a single isolated phytochemical may not have the same beneficial effect. Only by using combinations of phytochemicals can their effective and complementary mechanisms increase their benefits. The synergistic effect of these compounds may result in significant healing benefits for the lung, as previously observed with the hepatoprotective effect of apricots.

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ANTIBIOTIC-RESISTANCE MECHANISMS IN BACTERIA AND NEWLY ANTIBIOTIC DEVELOPMENTS

Nurcan BERBER

ANTIBIOTIC-RESISTANCE MECHANISMS IN BACTERIA AND NEWLY ANTIBIOTIC DEVELOPMENTS

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1. INTRODUCTION

Antibiotics represent great importance in the treatment and prophylaxis of infectious diseases caused by microorganisms in therapy pharmacy (Lin et al., 2015). Respectively in the 1930s and 1940s, successful clinical development of sulfa drugs and penicillins had a significant impact on the treatment of infectious diseases and significantly reduced mortality and morbidity (Yoneyama and Katsumata, 2006). However, almost simultaneously with the discovery of antibiotics, it is predicted that microorganisms can gain resistance to these drugs and that if the necessary precautions are not taken, the existing antibiotics will lose their effect in the treatment of infectious diseases and therefore humanity may face the pre-antibiotic period (Cohen, 2000; Gould and Bal, 2013). One of the interventions to prevent the clinical reflection of antibiotic resistance from reaching the feared dimensions is the discovery of new antibiotic drugs and a great development has been achieved in this area in a short time (Okeke et al., 2005).

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. The cause of antibiotic resistance is genetic mutation, or transfer of resistant genes from other bacteria, or also bacteria may be inherently resistant to an antibiotic naturally (Murakami et al., 2002).

2.Antibiotic-Resistance of Bacteria

Resistance mechanisms in bacteria can examined under two main headings;

2.1. Natural (phenotypic) resistance

This type of resistance is usually due to structural and biochemical properties depending on the nature of the bacteria (Shah et al., 2004). Bacteria showing resistance in this way are naturally the binding may not contain the target region, or naturally exhibit low permeability to them due to differences in the chemical structure of the antibiotics, or bacteria can also have natural resistance if the drug fails to reach its target due to a structural feature (Shah et al., 2004; Yüce, 2001). When both conditions there is no genetic modification; so it is called ″phenotypic resistance″. Phenotypic resistance may be characterized by just one or a few discrete states in the population up to a virtually continuous distribution of degrees of partial resistance. For example; Gram-negative bacteria are naturally resistant to the activity of macrolide antibiotics (Yüce, 2001; Tenover and Hughes, 1996). Bacteria show their natural resistance to the antibiotic in four different mechanisms, those are enzymatic inactivation, active pump system and changes in outer membrane permeability, changes in the target region of the bacteria and intracellular metabolic regulation (Cesur and Demiröz, 2013; Nikaido, 2009).

2.2. Acquired resistance

Acquired resistance can be the result of mutations in chromosomal genes or due to the acquisition of external genetic determinants of resistance, likely obtained from intrinsically resistant organisms present in the environment (Shao et al., 2015). This kind of resistance occurs due to changes in the genetic characteristics of bacteria

chromosome or extrachromosomal (plasmid, transposon, etc.) (Davies, 1994; Coates et al., 2002; Özturk, 2002).

Chromosomal resistance arise from mutations in developing in spontaneous bacterial chromosome (spontaneous). Such mutations may occur according to some physical (ultraviolet, etc.) and chemical factors. This takes place in one or more stages and can be a result of structural changes in bacterial cells. The result may be reduced permeability of bacterial drug or changes of the target of the drug may be in the cell (Yüce, 2001; Özturk, 2002; Jawetz et al., 2013).

Extrachromosomal resistance, depends extrachromosomal genetic elements that can be transferred in various ways like plasmids, transposons and integro. Plasmids are extrachromosomal DNA fragments. They are usually responsible for the generation of enzymes which inactive antibiotics. Resistance genes and plasmids carrying the genetic material from a bacterium in three ways those are transduction, transformation, conjugation, and transposition mechanism (figure 1) (Yüce, 2001; Cesur and Demiröz, 2013; Özturk, 2002; Jawetz et al., 2013; Džidić, 2008).

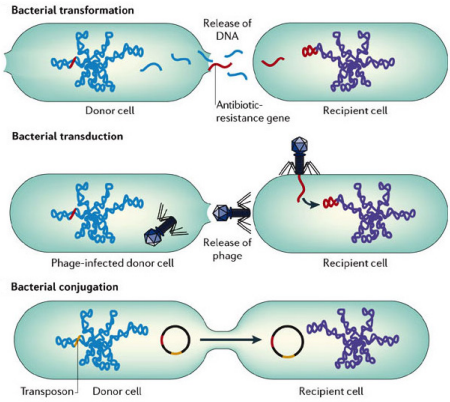

Figure 1. *The transport of genetic material from a bacterium in three ways (Furuya and Lowy, 2006).*

Bacteria are show that resistant to antibiotics with one of three ways (figure 2):

Prevention of access to target; antibiotics need to penetrate into the cell to act. One way this is the removal of the antibiotic out of the cell by active pumping. The development of resistance in microorganisms resistant to tetracycline is this way.

Changes in antibiotic targets by mutation; most antibiotics specifically bind to their targets with high affinity, thus preventing the normal activity of the target. Changes to the target structure that prevent efficient antibiotic binding, but that still enable the target to carry out its normal function, can confer resistance. For example; ß-lactamases inactivate these drugs by breaking down the amide bond in the ß-lactam ring of penicillin and cephalosporins.

Changes in the target of the antibiotic; the bacterium may gain resistance as a result of a change in the target of the antibiotic. The development of resistance as a result of the change in the target is one of the most common resistance mechanisms. For example; quinolone resistance to ciprofloxacin is caused by inhibition of the enzyme DNA gyrase (Billal et al., 2011; Gaoet al., 2010; Leclercq, 2002; Çiftci and Aksoy, 2015).

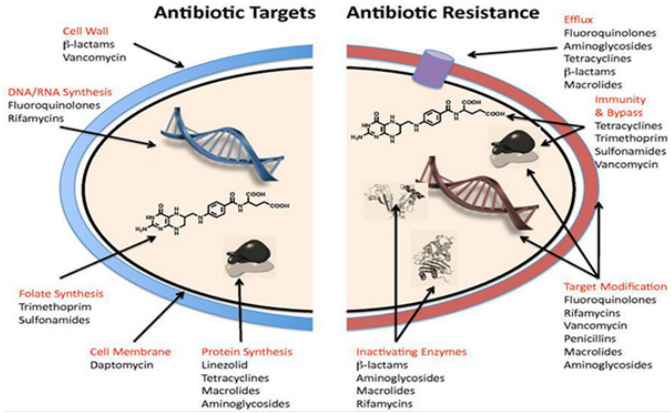

Figure 2. *Antibiotic targets and mechanisms of resistance (Wright, 2010).*

3. Antibiotic Specific Resistance Mechanisms

The discovery of the antibiotics and the distribution of the resistance of bacteria against antibiotics is given (figure 3).

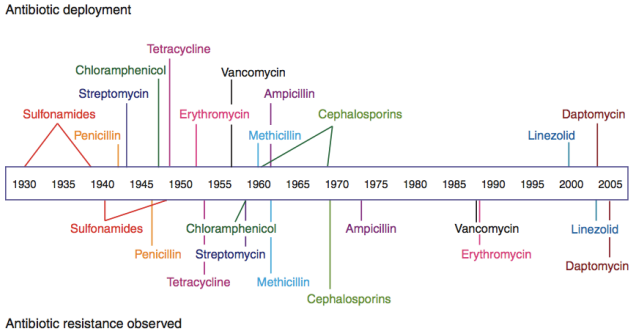

Figure 3. *Year of first use and then clinical resistance for each antibiotic (Clatworthy et al., 2007).*

3.1. β-lactams

Before the discovery of antibiotics, bacteria that cause lethal diseases such as septicemia (the presence of disease causing bacteria in the blood) have significantly reduced the quality of life. However, after the first isolation of penicillin in Oxford, the development of new antibiotics, similar to the penicillin structure, has been opened (Pal et al., 2007). Penicillin is the oldest known β-lactam derivative antibiotic. It is one of the oldest and most widely used and than is the first drug to be used against bacterial infections. It is also considered to be one of the safest and most effective antibiotic drugs from the β-lactam derivatives (Alekshun and Levy, 2007). Beta-lactam group antibiotics are the most widely used antibiotic group and distinguished from other antibiotics by common chemical molecules called ''β-lactam'' ring. This ring is sensitive to nucleophilic attacks. So, they exhibit biological (activity and inhibition) properties. This group of antibiotics consists of penicillins, cephalosporins, monobactam antibiotics and carbepenems (Verhaegen et al., 2003; Finberg and Guharoy, 2012; Brogden and Heel, 1986). β-lactam group antibiotics take charge in the stage of transpeptidation during bacteria‘s cell wall synthesis. it causes the suppression of the enzyme by binding to penicillin binding protein (PBP), also known as transpeptidase. The suppression of the enzyme leads to deterioration of the wall integrity and loss of resistance of the bacteria against the external environment (Džidić, 2008; Palomoet al., 2001; Venter, 2019). On the other hand, the affinity of gram-positive and anaerobic bacteria to PBPs is extremely low and therefore there is no effect of aztreonam against them (Verhaegen et al., 2003; Neu, 1990; Schaad et al., 1989). Generally, the resistance against β-lactams is the production of beta-lactamase enzymes in chromosome and plasmid control. Beta lactamase enzymes are produced by many bacteria of clinical importance. They can degrade

a wide spectrum of β-lactam antibiotics, sometimes also the last resort drugs available for infections with these bacteria. Nowadays, more than 200 different beta-lactamase enzymes have been identified (Bonnet, 2004; Nordfelth et al., 2005). Also, the resistance can develop as a result of the modification of PBP and decrease in permeability of outer membrane (Nordfelth et al., 2005; Akalin,1994; Muschiol et al., 2006).

3.2.Sulfonamides

The sulfonamides, the first antimicrobials developed for large scale introduction into clinical practice (in 1935), target dihydropteroate synthase. Their serendipitous discovery (the antibacterial activity was seen initially in vivo when the active compound was released as part of a dye) pales only in comparison with that of Fleming's chance discovery of penicillin (Levy, 2002). Trimethoprim, introduced in 1968, inhibits dihydrofolate reductase and was the last structurally unique antibiotic approved prior to the release of linezolid in 2000. Mutations in the gene specifying dihydropteroate synthase decrease the enzyme's affinity for the sulfonamides and have been found in laboratory experiments using E. coli and Streptococcus pneumoniae and in clinical isolates of Campylobacter jejuni and Haemophilus influenzae. Mutations in the chromosomal gene specifying dihydrofolate reductase can result in overexpression of an enzyme with a reduced affinity for trimethoprim and thereby offer very high-level trimethoprim resistance in E. coli and H. influenzae (Sköld, 2001).

3.3.Aminoglycosides

Aminoglycosides are a class of antibiotics used mainly in the treatment of aerobic gram-negative bacilli infections, although they are also effective against other

bacteria including Staphylococci and Mycobacterium tuberculosis. They are long post-antibiotic effects. Since the concentration-dependent effects are at the forefront, this group of antibiotics can be used as a single dose per day, and if necessary, the dose range can be opened. There are three main mechanisms of aminoglycoside resistance that are known: decreased cell permeability;alterations at the ribosomal binding sites; and production of aminoglycoside modifying enzymes. Permeability mutants have low-level resistance (Amunts et al., 2015).

3.4.Tetracycline and other antibiotic groups

Tetracyclines are one of the most widely used antibiotics in the world because they are a group of drugs with low toxicity, cheap and superior pharmacokinetic properties, especially doxycycline. They discovered in the 1940s. Both doxycycline and minocycline show excellent in-vitro activity to mycobacteria and staphylococci and are preferred to other tetracyclines in that they do not require dose adjustment in renal dysfunction (Chopra and Roberts 2001). The most well-known member of the glycopeptides, vancomycin, is effective against Gram-positive bacteria and penicillin-resistant staphylococci. The emergence of penicillins resistant to beta-lactamases such as methicillin, oxacillin, naphthyline has significantly reduced the use of vancomycin. However, with the emergence of methicillin-resistant staphylococci in the early 80s, the use of vancomycin became widespread. When we look at sulfamethoxazole and the combination of trimetoprene with sulfonamides, this combination of antibiotics has been widely used in synergy with Gram-positive and Gram-negative aerobic infections (González-Bello, 2017; Ghosh et al., 2017).

4. Challenges of Antibiotics Resistance and New Antibiotic Developments

Antimicrobial resistance is now a worldwide therapeutic problem. It is a growing global threat to human, animal and environmental health concerns. WHO's new Global Antimicrobial Surveillance System (GLASS) shows that diffusiveness occurrence of antibiotic-resistance among 500 000 people with suspected bacterial infections across 22 countries (World Health Organization, 2018). Annually, only in the USA antibiotic-resistant pathogen-associated hospital-acquired infections (HAIs) account 99,000 deaths (Infectious Diseases Society of America (IDSA), 2011). In the Europe more than 20,000 people are infected with antibiotic-resistant and that this costs the European Union economy €1.5 billion annually (World Health Organization, 2014; Hampton, 2013). Also, Antibiotics are widely used in food animals and it is estimated that such uses will increase to 67% in the crowded countries of the world, in 2030 (Van Boeckel et al., 2015).

Recently, the most notorious antibiotic resistant bacteria is S. aureus, and antibiotic resistant microorganisms including Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species have been identified as the so-called "ESKAPE" microorganisms which have caused important morbidity and mortality (Boucher et al., 2009). It is left to the research laboratories to provide solutions to this problem. One way of Innovation in antibiotic development is combination therapy. For this has been made by the use of β-lactams in combination with β-lactamase inhibitors. On the other hand scientists have focused on methods such as antibacterial resistance by nanoscience technology (Lasemi et al., 2016) or controlling bacterial antibiotic resistance using plant-derived or herbal medicines to reduce antibiotic resistance

(Kon and Rai 2016; Ribeiro et al., 2018). It is not surprising to the use of nanotechnology for the management of the antibiotic resistance menace.

Nanoparticles can be combined with available antimicrobial agents for increase their physicochemical behavior against drug-resistant microbes. they can not only combat bacteria themselves but can also act as carriers for antibiotics and natural antimicrobial compounds (Wang et al., 2017). They are used combine with different (bio) molecules such as Ag, Au, Al,Cu, Ce, Cd, Mg, Ni, Se, Pd, Ti, Zn, and super-paramagnetic Fe and this combination is most effective nanomaterial against bacteria (Hemeg, 2017; Slavin et al., 2017). They target the bacterial cell wall. For example, silver nanoparticles can be combined with the corresponding antibiotics to enhance their antibacterial effect by synergism (Kumar et al., 2018).

Natural plant products have proved to be a essential source of principle and have many extracts and compounds with antiviral activity (Vlietinck and Berghe,1991). Balasubramaniam et al. (Balasubramanian et al., 2007), reported that the antiviral activity of Indian medicinal plants against white spot syndrome virus (WSSV)in shrimp. Also, Pratiwi Wikaningtyas and Elin Yulinah Sukanda (Wikaningtyas and Sukandar, 2016) reported that antibacterial activity of plant extracts such as Curcuma xanthorrhiza(C. xanthorrhiza),Ocimum sanctum(O. sanctum),Senna alata(S. alata) against MRSA, ESBL-producing bacteria and CRE. Various studies have reported that antibacterial activity of plant extracts (Mostafa et al., 2018; Dzotam, J. K., et al., 2016).

5.Conclusion

In this context, we need to be more conscious topics such as rational use of antibiotics, use of antibiotics in

human and animal health, use of drugs and antibiotic use, importance of antibiotic resistance in food consumption, new approaches in antimicrobial therapy. The development of strategies for the use of rational antibiotics in all sectors and the use of the obtained data in the development of new antibiotics will be a positive step against antibiotic resistance.

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NEW GENERATİON, NEW EXPERİENCES İN ORAL ANTİCOAGULATİON

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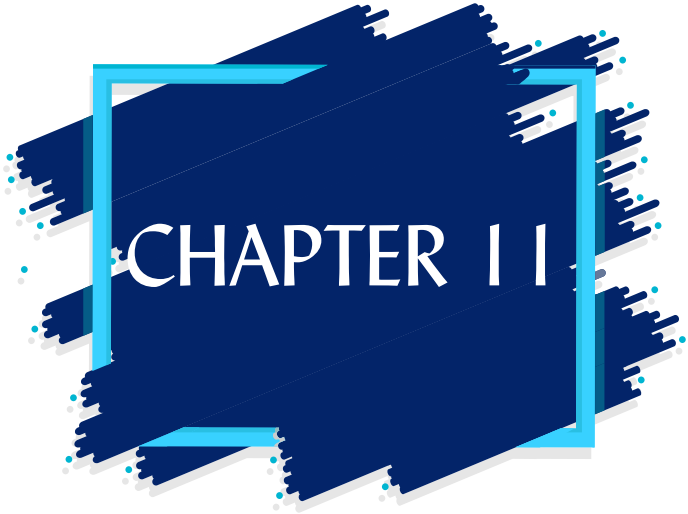

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INTRODUCTION

There are 2 types of venous thromboembolism (VTE): deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most common cardiovascular disease, with an incidence of 100-200/100,000. (1) Pulmonary thromboembolism (PTE) is a serious condition in which parts of a thrombus, most often occurring in the deep veins of the leg, break loose and travel to eventually occlude the pulmonary arteries or branches. In untreated cases, the mortality rate of PTE is approximately 25% to 30%, though the rate decreases to 2% to 8% in treated patients. (2) Chronic treatment of PE is at least as important as the acute phase therapy. VTE often recurs between the first 6 and 12 months. Overall (probable/definite) cumulative percentages of VTE recurrence have been reported as 10.1% (4.1%) at 180 days and 12.9% (5.6%) at 1 year, and the risk of relapse persists for at least 10 years after the initial VTE episode. (3) Anticoagulation is recommended to prevent premature death and recurrent symptomatic or fatal VTE in patients with acute PE. The duration of standard anticoagulation is at least 3 months. (1) Vitamin K antagonists (VKAs) have been the mainstay of anticoagulation treatment for over 50 years. However, limitations, such as food and drug

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interactions, bleeding complications, and the necessity of constant international normalized ratio (INR) follow-up have led to the use of direct oral anticoagulants (DOACs).

Current evidence suggests that DOACs have comparable or greater efficacy and safety results when compared with warfarin. (4) In this article, a case of pulmonary embolism and bleeding (hematuria and hemoptysis) occurring while under DOAC (rivaroxaban) use is described, and the efficacy and reliability of the new generation oral anticoagulants is discussed.

CASE

A 78-year-old male patient presented at the emergency department with hemoptysis, chest pain, and dyspnea. Three days prior, the patient had expectorated sputum mixed with bright red blood, and the quantity had increased to a volume of half a teacup within the previous 24 hours. He was experiencing chest pain and shortness of breath. He complained of hematuria ongoing for 5 days. There was no cough or fever.

He had experienced pulmonary tuberculosis 38 years earlier, coronary artery disease 5 years earlier, and ischemic cerebrovascular disease 3 years earlier. He also had hypertension, hypothyroidism, and benign prostatic hypertrophy. Five years prior, the patient underwent coronary angiography with the indication of non-ST ventricular tachycardia, and extensive left anterior descending artery calcification was observed. Oral drug treatment was initiated with 150 mg acetyl salicylic acid (ASA), 50 mg metoprolol, 200 mg amiodarone, and perindopril + indapamide (5/1.25 mg) He was left without treatment afterwards.

Three years before the current presentation, this patient with atrial fibrillation (AF) was followed up by the department of neurology for indications of an ischemic cerebrovascular accident. Upon the recommendation of a cardiologist, oral treatment with metoprolol (50 mg once daily) and rivaroxaban (20 mg twice daily) was initiated.

Echocardiography performed 3 years ago had revealed the presence of biatrial dilatation, Chiari network in the right atrium, 3° mitral regurgitation, 1° aortic insufficiency, 2-3° tricuspid insufficiency, and pulmonary hypertension.

The patient complained of feelings of distress and hot flushes after 1 month of rivaroxaban use, so he was switched to 150 mg oral ASA treatment. In an external center 2 months before presentation at our facility, his ASA treatment had been discontinued, and oral treatment with 20 mg rivaroxaban was reinitiated.

On systemic examination, no pathology was detected other than mild bilateral pretibial edema. Crepitant rales were auscultated over the basal parts of the lung during a pulmonary examination. Some important parameters were as follows: oxygen saturation in room air: 89-90%, platelet count: 139,000/mm^3, serum D-dimer level: 1.0 ng/mL, and INR: 1.6. Liver function test results were 5 times higher than normal. AF was observed on an electrocardiogram.

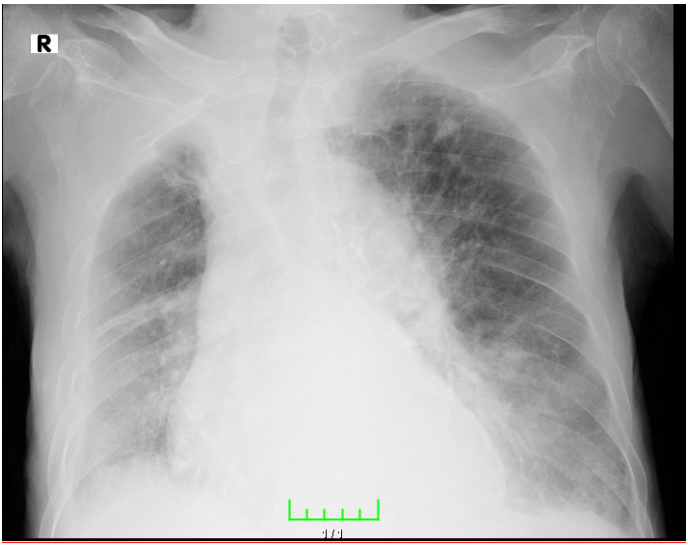

Figure 1: *Posteroanterior chest X-ray.*

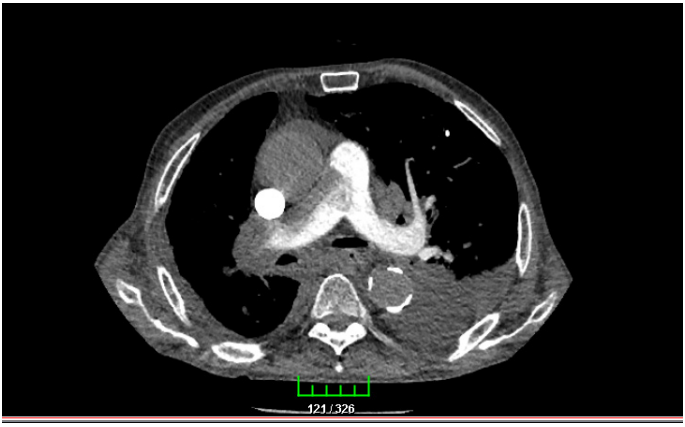

Figure 2: *Pulmonary angiogram.*

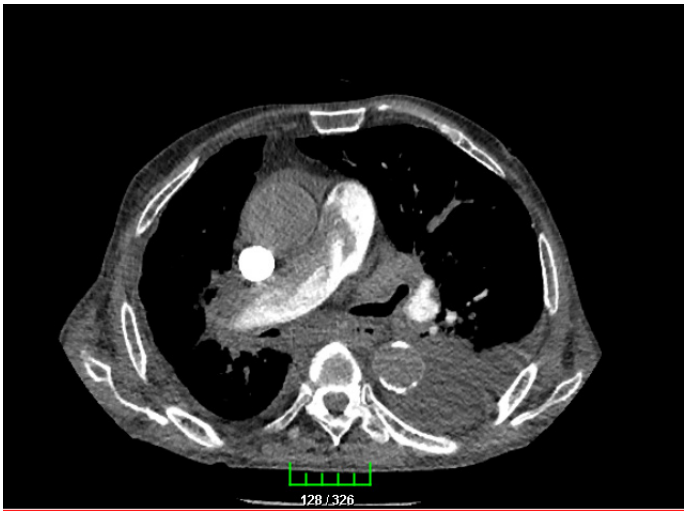

Figure 3: *Pulmonary angiogram.*

While in the emergency service, the cardiology department was consulted, and a bedside echocardiogram was performed, which revealed an ejection fraction of 35%. Acute coronary syndrome was not observed.

Pulmonary angiography demonstrated a filling defect in the right main pulmonary artery, and he was hospitalized in our service with the diagnosis of PE. Rivaroxaban treatment was discontinued in consultation with the cardiology department. Subcutaneous treatment with enoxaparin sodium (0.6 mL twice daily) was implemented. In addition to drug treatment, pantoprazole (40 mg, once daily), levodropropizine (30 mg/5 mL syrup oral [3x2]), and furosemide (20 mg intravenously once daily) were also prescribed.

A complete urinalysis was requested with the indication of hematuria. Oral ciprofloxacin (500 mg twice daily) was also started, as the patient also had a urinary tract infection.

Urinary system ultrasonography disclosed simple cortical cysts in both kidneys and trabeculae in the bladder wall. The urology department was consulted. Acute pathology was not observed.

A venous Doppler ultrasonogram of the lower extremities was obtained. Bilaterally, all veins demonstrated complete response to compression and the lumens were anechoic. Thromboembolism was not observed.

The patient had no additional pathology, and the hematuria and hemoptysis regressed. Since the patient was an elderly individual who lived outside the center of the city and couldn't undergo magnetic resonance image monitoring, apixaban treatment was initiated rather than warfarin. In accordance with pulmonary embolotherapy, apixaban was administered in twice-daily oral doses of 10 mg for 7 days, followed by doses of 5 mg twice daily. The patient was discharged with a recommendation for recommending polyclinic control. Observation and follow-up of the patient are still ongoing.

DISCUSSION

AF and VTE are common disorders associated with thrombotic events, especially in elderly patients. Due to the frequency of polypharmacy, comorbidities, and the altered pharmacokinetic properties of the elderly, the use of anticoagulants is very challenging (5). Until 2009, warfarin was the primary choice for anticoagulant therapy. Although the efficacy of VKAs in preventing thrombotic events is good, use has been limited in the elderly until now (6). Drug and food interactions are the major reasons limiting their use in older patients, as well as the risk of bleeding and the need for continuous monitoring.

Recently, 4 new oral anticoagulants (NOACs) have been developed to prevent thromboembolic complications in AF and VTE. These new anticoagulants inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban) in a dose-dependent manner. Rivaroxaban, apixaban, and dabigatran have different pharmacological properties and require guidance concerning the optimal doses and dose ranges, with consideration given to the presence of kidney or liver failure, age, diet, and other drugs used. (7)

Dabigatran, which is recommended for secondary prophylaxis, is an oral thrombin inhibitor with renal clearance. Dabigatran and warfarin were compared in the RE-COVER trial performed in 29 countries. The results released in 2009 indicated that any type of bleeding event was more frequently seen among patients in the warfarin group; however, there was no significant difference observed in the incidence of major bleeding. In the dabigatran group, a significantly greater number of patients experienced adverse events (hazard ratio [HR]: 1.33; 95% confidence interval [CI]: 1.01-1.76) and dyspepsia leading to discontinuation of the study drug (2.9% in the dabigatran group and 0.6% in the warfarin group). (8)

Rivaroxaban is a direct factor oral 10a inhibitor that is eliminated through the liver and kidneys. The recommended dose in the acute phase and for 3-week maintenance treatment is 15 mg twice daily and 20 mg once daily, respectively. (2) In the intention-to-treat analysis of the double-blind, randomized ROKET-AF rivaroxaban-warfarin noninferiority study, primary endpoints were reported as 2.1%/year in the rivaroxaban group and 2.4/year in the warfarin group (HR: 0.88; 95% CI: 0.74-1.03; $p<0.001$ for noninferiority; $p=0.12$ for superiority).

Clinically significant major bleeding occurred in 1475 patients (14.9%/year) in the warfarin group and nonmajor bleeding was observed in 1449 patients (14.5%/year) in the rivaroxaban group (HR: 1.03; 95% CI: 0.96-1.11; p=0.44) A significant decrease in intracranial and lethal bleeding was observed in the rivaroxaban group (0.7% and 0.5%, 0.5% and 0.2%, respectively; p=0.003) (9).

Apixaban is an oral factor 10a inhibitor recommended for 7 days at doses of 10 mg twice daily in the acute phase and 5 mg twice daily as a maintenance treatment. In the AMPLIFY study it was observed that apixaban was as effective as the standard treatment, and safer in terms of the risk of major bleeding. Major bleeding was observed at a rate of 0.6% under apixaban and 1.8% under the standard treatment (relative risk [RR]: 0.31; 95% CI: 0.17-0.55; p<0.001 for superiority). The composite outcome of major bleeding and clinically relevant nonmajor bleeding was seen in 4.3% of the patients in the apixaban group and 9.7% of those in the conventional treatment group (RR: 0.44; 95% CI: 0.36-0.55; p<0.001) (10) Furthermore, in the ARISTOTLE apixaban study published in 2011, apixaban was found to be superior to warfarin in the prevention of stroke or systemic embolism in patients with AF, leading to a lower mortality rate. The annual incidence of major bleeding was 3.09% in the warfarin group and only 2.13% in the apixaban group (HR: 0.69; 95% CI: 0.60-0.80; p<0.001). (11)

When meta-analyses concerning oral factor 10a inhibitor and standard anticoagulant treatment in the treatment of PE were compared, episodes of recurrent embolism were observed at a rate of 2.2% with the standard regimen and 2.4% with factor 10a inhibitor treatment, and the rate of all-cause mortality was 1.6% and 1.9%, respectively. (12)

We observed a complication of PE and minor bleeding in our case 20 days after the start of rivaroxaban following long-term ASA (coraspin). In summary, the new generation oral anticoagulants are advantageous alternatives for physicians, particularly in areas where standard treatment regimens cannot be applied due to the limitations of the standard treatment regimen. However, because the data are still insufficient and specific antidotes to neutralize bleeding effects, they are not yet first-line treatment alternatives for prophylaxis and the treatment of DVT, especially in elderly patients, oncology patients, and pregnant women.

CONCLUSION

One of the most important points in the choice of new generation oral anticoagulants is appropriate patient selection. It is also of great importance to increase our experience by adding to the existing data in order to establish the benefit-risk balance. In the coming years, we will see whether or not oral anticoagulation therapy with new generation drugs will supplant the use of VKAs.

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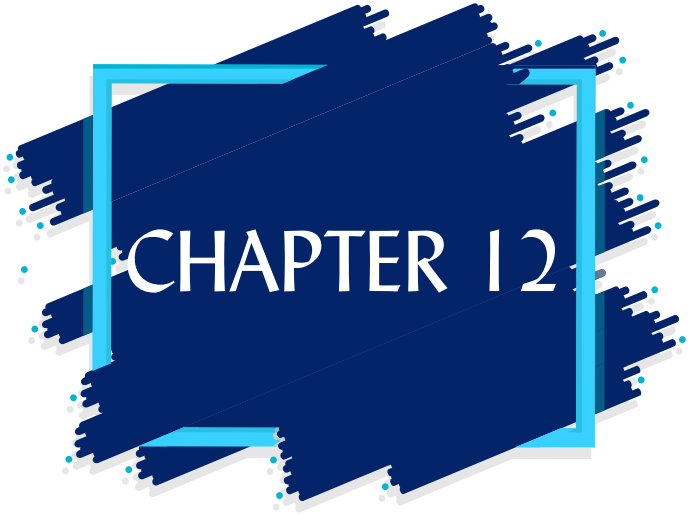
HUMAN MICROBIOTA AND MICROBIOTA RELATED DISEASES

Tuba SEVİMOĞLU[1], Özge GÜL[2]



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HUMAN MICROBIOTA AND MICROBIOTA RELATED DISEASES

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INTRODUCTION

Microbiota has recently become one of the most important research topics and human microbiome which comprise of bacteria, viruses, archaea, and eukaryotic microbes are found in various regions of our body and they affect our physiology. Microbiota contributes to metabolic functions, protects the body against pathogens and contributes to the immune system. The presence of pathogenic microbes or the absence of useful microbes or dysbiosis can cause various diseases. By investigating these microbes and making various analyzes, we can acknowledge how important microbes are in understanding diseases. These methods are currently under investigation as microbiota is transferred, for probiotic and prebiotic use. In addition, long-term antibiotics use, as well as factors that damage microbiota are being investigated.

In the human body, there are bacteria, viruses, and microbial eukaryotic communities that are specific to each anatomical, e.g. the gastrointestinal tract, the skin, the vagina and the mouth (1). The human microbiota consists of approximately 100 trillion microorganisms. Each body region carries its own characteristic microbial communities (2).

Various microbial communities are needed for many basic processes such as maintaining pH balance in the mouth and vaginal cavities, preventing the settling of pathogenic organisms in the body, stimulating the immune

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system, assisting digestion and providing the nutrients necessary for our body health (3). Identifying the regions in which these communities are located on the human body is important in determining health criterion for detecting differences in diseases (4).

The microbiota does not only vary by human body parts, it also varies depending on time, countries, world regions and feeding patterns (4-6).

1. TERMS OF MICROBIOTA

It is important to understand the terms related to microbiota such as microbiome, metabolite, dysbiosis, some analysis techniques and Human Microbiome Project (HMP).

Microbiome is the collection of genes and gene products (RNA, proteins, metabolites) produced by resident members of a microbiota. This term was named by the Nobel Laureate Joshua Lederberg (7).

Human microbiome directly impresses many aspects of human physiology such as metabolism, drug interactions, and being a factor in certain diseases (8).

Metabolite is a small chemical that is a product of metabolic action or that is involved in a metabolic process (9). They are the intermediate products of metabolic reactions catalyzed by several naturally occuring enzymes within cells (10).

Some example of metabolites are; SCFAs (Short Chain Fatty Acids), Tryptophan metabolite, Retinoic acid (RA). Metabolites are very crucial for immune system development and differentiation (11). They also trigger anti-inflammatory response and regulates symbiosis as well (12).

Dysbiosis is described as "any change in the composition of the microbiota that might cause damage to the host often through extrinsic pressures like disease, medicine or change in diet as well as stress (13, 14). It is substantial to understand the relationship of dysbiosis to diseases considering the knowledge obtained from the relationship between microbiota and dysbiosis wil also affect what can be done to prevent dysbiosis-induced diseases.

A variety of analysis techniques such as 16S sRNA, culture, and omic techniques are used in understanding the affects of microbiota on disease and health. Each analysis technique has its own advantages and limitations. Researchers should determine the best technique based on the problem they want to address. The most commonly used analysis techniques are omics techniques such as metagenomics, transcriptomics, proteomics and metabonomics (15).

Metagenome allows us to learn about the potential function of microbiota. *Metagenomics* is a procedure used to characterize the metagenome (16). Metagenomic sequencing does not only define which microbial groups exist. It can also detect the plenty of several bacterial genes and functional pathways in a microbial community (17).

Metabonomic describes the dynamic responses in the metabolism of living systems to pathophysiological stimulants or genetic alterations as measured quantitatively (18). Thus, a lot of information about metabonomically diverse molecules can be produced. Further, variations in biological processes can be measured as a result of diverse nutritional reactions. Examples of the use of metabonomics include toxicity screening, drug metabolism, and functional genome research (19).

Metabolomics involves analysing the metabolites produced by a microbial community (20). It proposes a speedy approach to characterize a good many small molecules linked to a sample (21).

Metatranscriptomics is an approach that can be used to study functional aspects of microbiota at transcriptional levels (22). Metatranscriptomic techniques are used to investigate gene expression of microbiome (23).

Metaproteomics is a method that directly measures the expressed proteins (24). This technic ensures functional information to the analyst to oversea alterations in protein expression by the microbiota (25). Each omic analysis technique has different approaches and advantages over each other and each of them help us in understanding the association of human health, and microbiota.

The Human Microbiome Project (HMP) was launched by the National Institutes of Health to investigate microbial flora. Together with advances in DNA sequencing technologies, a metagenomic approach has been used instead of conventional microbiology techniques to study microbial populations in HMP. The HMP targets five body areas to carry out focused studies: the gastrointestinal tract, oral cavity, vagina, skin and the nasal passage.

The HMP studies the human microbiome, not only the single bacterial genome in humans but also the microbiome population, including population diversity, etc. They have created a dynamic project catalog with HMP. Catalog is revised on a regular basis as new organisms are nominated for inclusion and move through the sequencing process (26).

2. TYPES OF MICROBIOTA

Many anatomical parts of the human body have their own microorganism variety. Types of microbiota are usually classified into skin, blood (plasma), lung, urogenital and gastrointestinal tract including oral and dental, esophageal, stomach and gut microbiota.

The microbiota has an important role in carrying out various roles in various parts of the body. When dysbiosis occurs in the microbiota of these regions, various diseases can be exposed. Some diseases may occur in the absence of beneficial microbes, and some may occur in the presence of pathogenic microbes.

The gastrointestinal tract (GIT), from mouth to anus, represents the most diverse, complex and delicate microenvironment in the mammalian body (27). The gastrointestinal tract consists mainly of the following organs: Mouth, esophagus, stomach, pancreas, liver, gut (small intestine and large intestine) and anus (28). Gastrointestinal microbiota mainly consists of the following sections: Oral and dental microbiota, esophageal microbiota, stomach (gastric) microbiota and gut microbiota (Figure 2.1).

According to microbiological point of view GIT can be considered as one of the best researched microbial ecosystems in the world. The majority of microbial genes and microbial diversity are located in human GIT (29). The highest microbial mass in the GIT is found in the distal gut (colon). Studies on the gut are also more extensive. Due to the easy access to sampling.

The human GIT has a large microbial mass containing about 10^{14} microorganisms of up to 1200 different species. Although bacteria are predominant in human GIT

microbiota it includes eukaryotic and bacterial viruses as well as fungi and archaea (30).

The human GIT microbiota consists of three habitats - Bacteria, Archaea and Eukarya. The bacteria in the adult GIT is rich in of the *Actinobacteria, Bacteroidetes, Firmicutes* and *Proteobacteria* phyla (31). *Candida* is the most common fungal genus and the most frequently proclaimed Archaea in the GI tract is *Methanobrevibacter* (32).

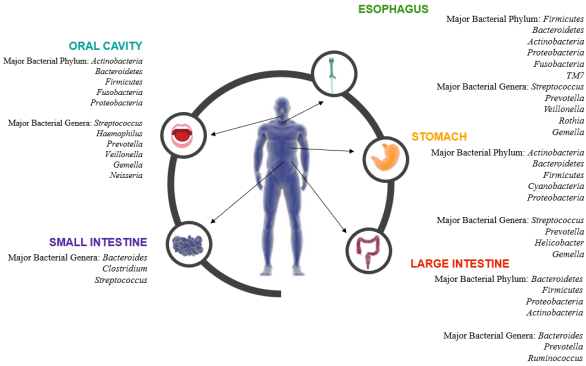

Figure 2.1: *Major bacterial microbiome composition of the human GIT. Major bacterial phylum and genera in the gastrointestinal tract(32).*

The most well characterized microbial populations in human microbiota, have a wide variety of intestinal and oral microbiota due to the ease of sampling. In the oral cavity, which has a critical function for protection from external bacteria, there are various diseases caused by microorganisms such as gingivitis, caries and periodontitis (33,34).

The oral microbiota is the densely colonized body site after the colon. The human oral cavity is colonized by bacteria, archaea, viruses, protozoa and fungi. Normal oral

microbiota is of importance, in helping prevent infection by exogenous pathogens, and is also important in nitrate metabolism, which is essential for cardiovascular health (35-37). The most common bacterial diseases in humans associated with oral microbiota are dental caries and periodontal disease (38).

Bacteria are the most predominant type of microorganisms in the mouth. Saliva contains around 100 million bacteria per ml and the inner surface of the mouth is covered by a bacterial biofilm. Oral microbiota of mammals contains the acknowledged *Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, Spirochaetes, Fusobacteria, Tenericutes* and *Chylamydiae.* And it contains the less recognized phyla or candidate divisions such as *Synergistetes, Chlorobi and Chloroflexi phyla* (39).

The esophagus is a muscular conduit of approximately 20–27 cm in length, with an internal mucosa (40). 16S rRNA gene studies identify existence of six main phyla (*Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria* and *TM7*) of microbes in this passage with *Streptococcus* being the most dominant (41).

The stomach is part of the upper gastrointestinal tract and it blocks the ingested microbes, affecting the microbial ecology of the entire GIT. Bacterial viable counts may be due to various factors such as the actual gastric pH, ethnicity or diet (42,43). The acidity of the gastric environment (pH <4) inhibits the growth of bacteria, so the stomach has the lowest number of microbes (44).

Despite the harsh acidic and antimicrobial environment, the gastric bacterial community is governed by five major phyla: *Proteobacteria, Actinobacteria, Bacteroidetes,*

Firmicutes and *Fusobacteria* (45). The stomach microbiota might contribute to diseases such as gastric cancer.

The main interaction investigated in studies on gastric microbiota is Helicobacter pylori (H. pylori) due to its relationship with gastritis, peptic ulcer and gastric cancer (46,47). Other common species are *Streptococcus* and *Prevotella*, both of which are also found in the oral and esophageal communities (48).

The final gastrointestinal microbiota is gut (also called intestine, intestinal) microbiota. The greatest microbial biomass in humans is in the GIT (49). Approximately 70% of all bacteria prevails in the colon (50). The number of species range from 400 to 1,500. The major bacterial phyla of the human gut are *Firmicutes, Proteobacteria, Actinobacteria, and Bacteroidetes* (51). Despite improvements in the analysis techniques, it would take time to form a stable taxonomic list with a suitable designation for all species in the gut.

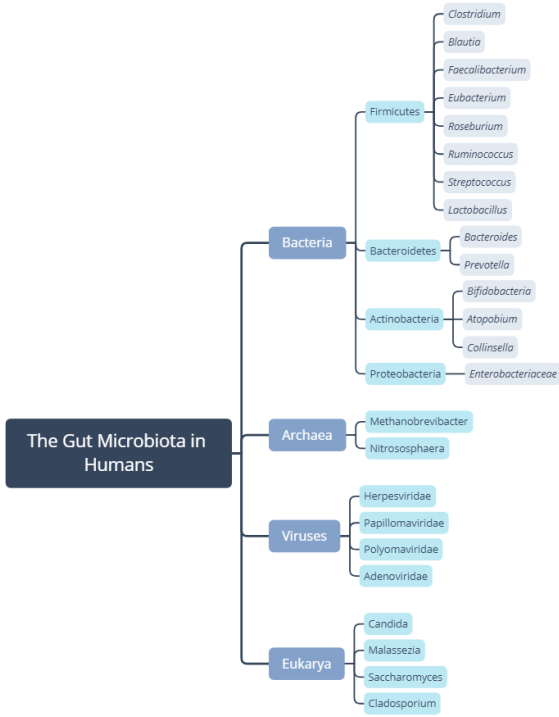

Figure 2.2: *Major taxa and the most common bacteria phyla and genera of the gut microbiota in humans (51,53);*

Color of taxa: , Color of phyla: , Color of genera:

There was a time when the blood stream was believed to be a sterile medium. However approximately 41 years ago Tedeschi et al. (1978), found bacterial DNA samples in their blood samples (54). Recent studies have confirmed blood microbiome. One of the sources of these microbes in the disease state is the gut microbiome in dysbiosis and microbes carried from the oral cavity (55,56).

The human skin is one of the largest organs of the body. It acts as a protector amidst the inner part of the body

and the external environment. Various active microbiota estimated at about 10^6 has settled in this area (57,58). Skin microbiota is linked to some serious skin diseases and wound infections, as well as contributing to the defense system of the skin.

Dysbiosis occurring in the skin microbiota might be instrumental in inflammatory skin diseases such as psoriasis, atopic dermatitis and acne vulgaris (59).

Another type of microbiota is the lung microbiota. Analysis of lung tissue samples demonstrates some 10 – 100 bacterial cells per 1000 human cells (60). The microorganisms of the lung microbiota might promote diseases like asthma. The predominant phyla are *Bacteroidetes* and *Firmicutes* in humans that have healthy lung (61-62).

The last type of microbiota is urogenital microbiota. This type of bacteria provides antimicrobial defense against urinary tract infections in the male and female urogenital tracts (63).

Vaginal microbiota is in the lower reproductive system of women and plays a crucial role in protection from infectious diseases. In contrast with the female urogenital tract microbiome, the composition of the penile microbiome and its significance to health is poorly understood (64).

3. MICROBIOTA RELATED DISEASES

Dysbiosis in the microbiota may cause diseases for instance in the absence of beneficial microbes, in the presence of pathogenic microbes.

3.1. Skin Microbiota Related Diseases

The skin is open to the external environment and is regularly exposed to microbial organisms. Pathological changes in the skin may alter the structure and roles of the skin microbiota. The change of microbiota can also affect the health of the skin and the condition of the disease. Dysbiosis in the skin microbiota can cause diseases such as acne, atopic dermatitis and psoriasis (65,67).

Research conducted on the relationship between skin microbiota and various skin diseases have shown that there is a boost of pathogenic bacteria along with the disease and a decline in the number of some beneficial bacteria (68-70).

3.2. Blood (Plasma) Microbiota Related Diseases

Dysbiosis in the microbiota can disrupt homeostasis and, as a result, can lead to disease development and progression. Blood microbiota might contribute to atherosclerosis, cardiovascular disease and type II diabetes, and thus are used as markers for cardiovascular disease (71-73).

H. pylori in the gastric mucosa may also be present in the blood and may contribute to pathologies preceding Parkinson's disease (PD) or motor symptoms (74,75).

In spite of the studies conducted, studies in this area have not progressed as much as other microbiota-disease examinations because the blood is thought to be mostly sterile.

3.3. Lung And Airway Microbiota Related Diseases

Since the lungs are in contact with air, they are exposed to microbes and cigarette smoke. This may cause short or long-term deterioration of the normal airway function. In such cases, long-term deterioration of host defense may lead to chronic infections of the lung with tobacco cigarettes, for example, leading to chronic obstructive pulmonary disease (COPD) in some cases (76).

A crucial consideration that affects the diversity of the lung microbiota is that the lung is constantly in contact with the outside air. The microbes in the air can enter the airway with breathing and affect the variety of microbiota in the lungs (77).

When chronic lung infections develop, the microbiota composition at the site of the infection is altered by a number of factors. These include the nature of the airway clearance impairment or airway damage that has led to infection. According to the results of studies on lung microbiota, pathogenic microbes in the airway and lung cause various diseases such as asthma, cystic fibrosis and COPD (78-80).

Taking into account the difficulty of sampling from the lungs, it becomes difficult to identify the microbes in the lung and airway microbiota and to understand their relationship to diseases. Despite these difficulties, studies reveal the relationship between lung and airway microbiota and various diseases.

3.4. Gastrointestinal Microbiota Related Diseases

Dysbiosis of the oral microbial flora can cause oral diseases like caries, oral cancer, mucosal diseases, peri-

implantitis and periodental diseases such as gingivitis and periodontitis. The role of periodontal disease in various intrinsic diseases such as diabetes, rheumatoid arthritis, cardiovascular disease, adverse pregnancy outcomes, and head-and-neck cancer is being investigated (81-83).

Research in the area of Esophageal Microbiota is relatively new compared to other microbiota studies and is thought to be associated with diseases such as gastroesophageal reflux disease, Barrett's esophagus, eosinophilic esophagitis, esophageal cancer and esophageal motility disorders (84-87).

Helicobacter pylori is part of the stomach microbiota in most of the humans. H. pylori is a factor in peptic ulcer disease, gastritis and development of adenocarcinoma (88-91). Apart from the studies carried out with H. pylori, there has not been much research on the function of gastric microbiota in other disorders.

Studies conducted to examine the link between gut microbiota composition and various diseases have shown that most of these diseases are clearly caused by microbiota dysbiosis e.g. Crohn's disease and ulcerative colitis (92,93).

Another group of diseases associated with gut microbiota are the autoimmune diseases. Autoimmune diseases are caused by the destruction of body's own healthy cells and tissues by the immune system. Dysbiosis might be an underlying cause. Many studies have been carried out on this subject (94-96). Other diseases related to gut microbiota are obesity, type 2 diabetes and colorectal cancer (97-99).

3.5. Urogenital Microbiota Related Diseases

The most studied disease in the urogenital microbiota is: Bacterial Vaginosis (BV). It is the highest prevalent urogenital tract condition of reproductive women (100). Women with this disease have excess concentrations of *Gardnerella vaginalis*, anaerobic gram-negative rods belonging to the genera *Porphyromonas* and *Bacteroides, Prevotella, Ureaplasma urealyticum, Peptostreptococcus species, Mycoplasma hominis*, *Mobiluncus species* in their vaginas (101).

4. POSSIBLE TREATMENT METHODS

Unbalance in microbiota might lead to various diseases as mentioned previously. Various methods and nutrients are used for the elimination of microbiota disorders. These foods are probiotics and prebiotics. Fecal transplantation method is important for the improvement of intestinal microbiota. These healing methods are mostly based on the principle of placing the so called good bacteria in the intestinal microbiota and multiplying their numbers.

4.1. Probiotics

Probiotics are defined as ‘live microorganisms which when administered in adequate amounts confer a health benefit on the host’ (102). They are available in many different types (in Table 4.1).

Table 4.1: *Different types of probiotics on the market (103)*

Naturally Fermented Products	Cheese, fermented milk, yogurt, butter
Not Fermented Food Products	Bread, biscuits, cereals/chewing gums, coffee, cookies, chocolates, chocolate bars, frozen yogurt, granola bars, honey, ice cream, ice tea, juices, muffins, pizzas, royal jelly, tea Breast milk, soy milk
Food Supplement Products	Dietary supplements provided as powders, (chewable) tablets, pills, capsules, straws (sticks)
Registered Pharmaceutical Products	Tablets, pills, capsules, vaginal suppositories
Cosmetics and Hygiene	Aftershave, anti-aging serum, face and body lotion, hydrating cream, toothpaste, sanitary napkins, tampons, shampoo, douche gel, oral care gums
Others	Household cleaner (floor & carpet), mattress, mattress protector, industrial wastewater treatment, bioremediation efforts, odor control solutions
Animal Applications	Digestive supplements and oral care for pets, grass protector (dog urine neutralizer), fish care products, Food supplements for commercial farm animals (poultry, pigs, horses, etc.)

Numerous studies of probiotics have demonstrated the potential of probiotics in health benefits in preventing many diseases. The characteristics of bacterial strains to be considered as probiotics have been defined (104).

First, these strains must reach their site of action, usually the gut. For this, they have to survive the physiological stresses met during ingestion, which include gastric and gut acidity and the presence of biliary salts. Second, they must have a proven beneficial effect. Third, they must not possess any risk for the host. Finally, they must keep all their characteristics and remain stable throughout the

manufacturing process and storage in the matrix in which they are incorporated (105).

Specific probiotic strains shown to have health benefits are; *Lactobacillus, Bifidobacterium, Saccharomyces, Leuconostoc, Enterococcus, Pediococcus, Streptococcus, Bacillus, Escherichia coli* (106).

4.2. Prebiotics

A prebiotic is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health" (107).

Gastric acidity and hydrolysis resistance, intestinal microbiota fermentability and the ability to trigger production or activity of good bacteria are the three criteria for prebiotic effect (108).

The most common prebiotics are fructo-oligosaccharides, galacto-oligosaccharides and trans-galacto-oligosaccharides. They naturally exist in different dietary food products such as garlic, onion, human's and cow's milk, honey, etc., and recently, seaweeds and microalgae (109).

4.3. Fecal Transplantation

Fecal transplantation is the direct application of fecal solution taken from a donor into recipient's intestinal system to alter and benefit the intestinal microbial composition of a recipient. It is mostly used in treating recurrent or refractory Clostridium difficile infection (CDI) (110). In a study of fecal transplantation to treat C. difficile infection, the results showed that microbiota could be improved by transferring it to a healthy microbiota (111).

5. CONCLUSION

There are millions of microbial organisms in the human body. These organisms are colonized in various parts of our body. The number and diversity of microbes varies according to the various anatomical regions of the human body. However, the microbiota does not only vary according to the human body. As can be seen in various studies, microbiota varies according to time, countries, world regions and diets. Therefore, cultural differences and environmental factors are taken into consideration in studies on microbiota.

The studies on microbial organisms in our body have focused on the disease-causing effects of microbes for a long time. However, with the development of various analysis methods, it was understood that microbes are important in health as well as disease. The importance of a healthy intestinal microbiota, especially with the effect of nutrition, has been clearly demonstrated by studies. In addition to the intestine, microbial communities in various parts of our body affect our body in both disease and health. The deterioration of the number and diversity of these microbes, the presence of pathogenic microbes and the lack of beneficial bacteria cause various diseases. Many studies on microbiota demonstrates that microbiota is instrumental in both disease and healthy states.

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THE POTENTIAL USE OF MIRNA BASED THERAPEUTICS IN ALZHEIMERS DISEASE AND AUTISM

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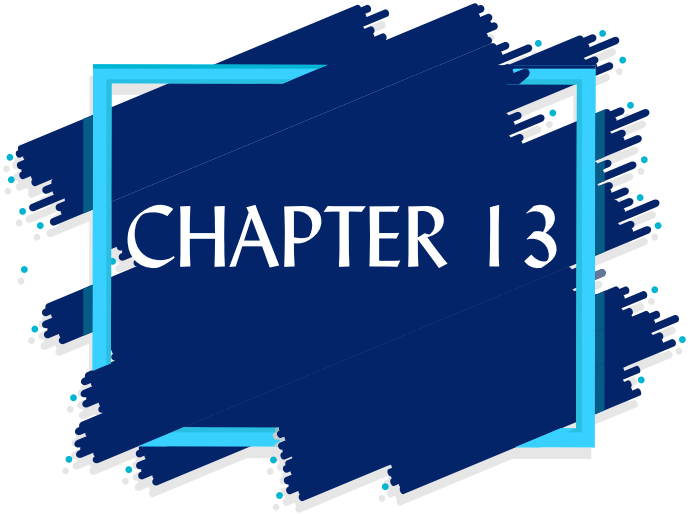

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THE POTENTIAL USE OF MIRNA BASED THERAPEUTICS IN ALZHEIMERS DISEASE AND AUTISM

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1. INTRODUCTION

Neurodevelopmental disorders (NDDs) are complicated conditions characterized by disruptions in cognizance, connection, behaviour and motor abilities because of uncommon brain improvement. They include recognizably diverse syndromes known to be inspired by many unusual variations in certain genetic loci. The phrase NDD may also indicate disorders that are frequently present in the society, such as schizophrenia, autism spectrum disorders, epilepsy, mental delay and communication disorders. After years of disappointment, previous couple of years have abruptly seen immense advancements figuring out the genetics of these irregularities [1]. NDDs are extremely widespread .Genetic, epigenetic, and environmental agents play a key role in NDD pathogenesis. Animal models are an essential tool in studying these disorders. Presently, there is no unique biomarker to define Neurodevelopmental disorders. Rather, these diseases are classified into separate groups.

Many symptoms are not specific to NDD and several NDDs contain common symptoms. For instance, disrupted social cognition is widespread to schizophrenia and ASD, and psychosis is common to schizophrenia, bipolar disorder and major depressive disorders. Therefore, these mutual clinical signatures make it difficult to run a therapy for each specific disease.

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2. Neurodevelopmental Disorders

For this chapter, only Autism and Alzheimer's diseases are handled.

2.1 Autism

It is likely that autism has existed since ages, but the first clinical data of this disorder are defined by Leo Kanner published in 1943. Dr. Kanner developed the primary kid psychiatry station in the USA. He described the important features of autism and all of these features are reflected in the current autism diagnosis guidelines. In Kanner's study, it is pointed out that the rate of autism in men is much higher than that of women.

Hans Asperger is an Austrian paediatrician. Asperger was working at nearly the same time as Kanner with a similar group of children. Asperger's syndrome, a lighter form of autism, was named after Hans Asperger.

As the word 'spectrum' implies, different forms of autism have different abilities and barriers, at mild and severe levels. A spectrum means that there are many varied ways that an ASD affects any person with that diagnosis. Each person with an ASD has different issues and different strengths. This makes an ASD complex.

For instance, a person may not have any functional conversation, or the vocabulary might be too advanced. He or she may be mentally disabled or have an IQ above the average. He may be an introverted person or, interestingly, might be socially very active. He may be obsessed with placing his toys in a specific order, or he may become obsessed with having encyclopaedic knowledge of cars or any favourite topic.

Autism is, in general, a lifelong situation coming about in childhood and with pathological consequences in adulthood. Consequences are often characterized as difficulties or issues in finance, employment and socialization.

ASD is generally composed of a bunch of heterogeneous neurodevelopmental states. There are 3 specific symptoms: Disrupted Communication, Constricted interests, and Recurrent and stereotypical behaviour pattern. Core symptoms for autism can be listed as social communication challenges and limited, repetitive attitudes. These symptoms arise in early childhood (though they might go unrecognized) which persist and interfere with daily living.

DSM-5 [2] is the list that healthcare providers use to diagnose mental and behavioural circumstances, with the inclusion of autism. According to DSM-5 criteria to diagnose ASD can be seen in Figure 1. Characteristics of Individuals with ASD can be seen in Figure 2.

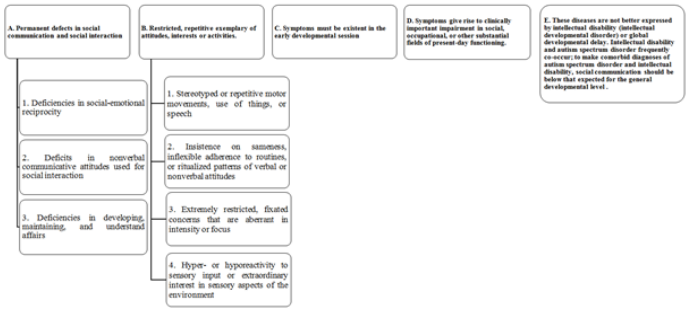

Figure 1: *List to diagnose ASD according to DSM-5 criteria [2]*

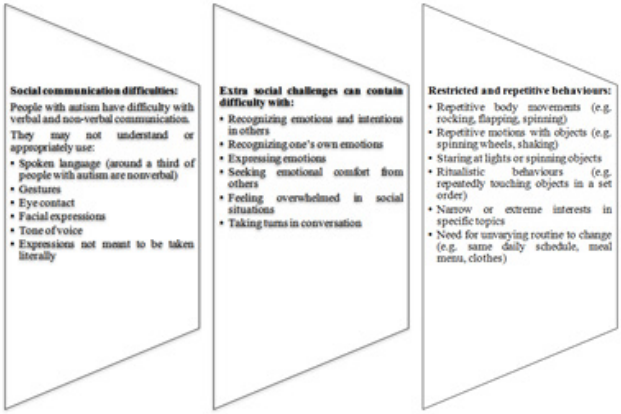

Figure 2: Characteristics of Individuals with ASD [2]

Classical Autism is the most substantial form of ASD. It is also called ‘’severe autism’’,’’Kanner’s Syndrome’’ and ‘’Autism Disorder.’’ A person with classic autism exhibits significant problems with speech, behaviour, and social interaction. Classical autism can be observed in children as well as adults (Figure 3).

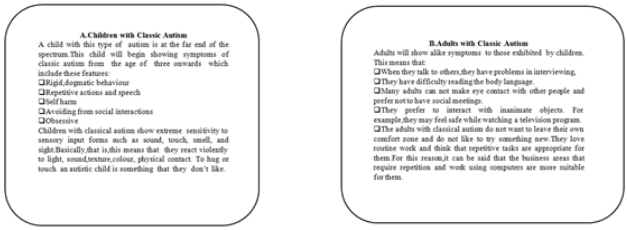

Figure 3. *Children and Adults with Classic Autism [3]*

According to the fourth edition of DSM5 published in 2000 there are two primary diagnostic criteria that must be present to ensure the determination of AS. One criterion relates to qualitative impairment in social interaction. Specific characteristics may include marked delays

in nonverbal behaviours, corruptions in establishing fellow relationships, absence of shared affection or accomplishments with others, and lateness in social cooperation.

The second criterion relates to limited areas of concern and stereotyped behaviours. Characteristics may include a preoccupation with a narrow space of interest, stability or rigidity, stereotyped or recurrent motor motions, and preoccupations with objects or parts.

As highlighted by Nayate et al. (2005), additional characteristics such as poor motor skills and sensory difficulties may also be evident. As further stated by Myles and Simpson (2002), there is some dispute over the presence of motor delays with AS, though there appears to be sufficient evidence to indicate potential problems in this area. For instance, Miyahara et al. (1997) conducted a study in which the that students with AS demonstrated a high prevalence of motor delay on a standardized test of motor performance [4-7]

Some of the aspects of Asperger's syndrome that differ from autism are:

- They are aware of what is going on around them.
- They experience more motor skills problems, such as riding a bike.
- They are very successful in mathematical operations and have a great memory.
- They are calm and always dream.

People who do not comply with any of the certain types of autism, like autistic disorder, Asperger syndrome

are said to have Pervasive Developmental Disorder (PDD-NOS). It is also called Atypical Autism.

PDD-NOS actually differs from childhood autism due to its failure to meet diagnostic criteria. PDD-NOS is only used in the cases where aberrant and disrupted progression occurs after the age of three, and there is no sufficiently demonstrable abnormality in one or two of the three psychopathologies necessary for the diagnosis of autism (In other words, mutual social relations, communication skills, and restricted, stereotyped repetitive behaviours). PDD-NOS appears most frequently in extremely retarded people and in people with a heavy particular developmental disease of receptive language [8].

One of the controversial subjects in the ASD research includes the sorts of therapies that are used and how they are chosen [9]. Drug treatment, for instance, is mostly used even though few data consists to assist usage of it, particularly the main symptoms of the disease. Additionally, these medicines are known to have severe side effects [10].

There is also a discussion about the influence of antipsychotic remedies to challenge attitudes midst people with developmental disabilities [11]. Furthermore, many psychological methods are also present [12]. A lot of these methods are labour-intensive and include parental involvement, which oftentimes is infeasible because of time restrictions or contrasting other pledges [13]. The number of research on what works is widening quickly. Besides, expert communities and state health squads have looked at present interference and advanced protocols on suggested therapies. So far, these attempts have not resulted in acceptable results [14].

In addition, independent studies have shown that mumps, measles and rubella vaccines have no effect on the progression of ASD. Nevertheless, vocal groups inside of the ASD society keep on to persist on the MMR vaccine being a reason for ASD which results in an amount of unvaccinated kids. Children who are not sufficiently vaccinated have a higher risk of preventable infectious diseases [15].

2.2 Alzheimer's Disease

Alzheimer's disease (AD) is one of the frequent difficulties for aged people. It has influenced an estimated 15 million people worldwide and expected to increase to 80 million. It is a complex intricate disease caused by both environmental and genetic factors. These elements give a start or raise the risk of developing AD. It is the sixth top-line reason of all deaths and the fifth leading reason of death in people aged ≥65 years [16]. The disorder is generally destructive in onset and increasing in severity little by little, but steadily, over a period of a few years [17]. been diagnosed with AD, s/he can survive with the disease, on average, 4 to 8 years before passing away (AA, 2013).

According to Reitz and co-workers (2012), up to now, a forecasted 5.4 million Americans have Alzheimer Disease, but owing to the baby boom generation, the ratio in 2050 is estimated to arrive a million people per year, following in a whole estimated universality of 11 to 16 million affected people [18].

The clinical agent's available developing corruption in memory, decision making, orientation to physical surroundings, and speech [19].

Alzheimer's disease consists of 2 subgroups. These are Early-onset (EOAD) and Late-onset (LOAD). EOAD situations are inherited in an autosomal dominant sample. LOAD as the most widespread form of Alzheimer Disease in the population (90 percent) takes place individually and is set up late in lifetime. In this case, dominant mutations in genes such as APP, PSEN-1, and PSEN-2 have been associated with Alzheimer's disease [20].

According to 2OO9 Progress Report on Alzheimer's disease, it is an age-related brain disorder and progresses over the years. The signs are usually seen after age 60. Every case is different however in many individuals, the earliest symptom is the loss of memory. As the disease progresses, individuals often experience problems with cognitive functions, such as decision-making and language skills, after memory decreases. These individuals also have a tendency of behaviour and character changes. The loss of mental abilities as the disease progresses affects the way of life and also deteriorates the ability to recognize friends and family. These losses are related to the breakdown of the linkages between diverse classes of neurons (nerve cells) in the brain and the incorporated death of many of these cells.

The costs of AD are meanwhile immensely individual and extensively societal. Family, friends and carers who see their loved ones becoming more and more forgetful and pensive have difficulties both emotionally and financially. When people with Alzheimer's disease lose their ability to live independently, family members have difficulty in caring [21].

People with Alzheimer's disease often go to living facilities established for care and assistance and then to nursing homes. As the population ages, it is expected that there will be an increase in the number of people with Alzheimer's disease, and naturally, there will be an increase in the number of caregivers [22].

Alzheimer's disease is a gradual neurocognitive condition that becomes worse in time. It includes a progressive loss of memory, as well as modification in behaviour, thinking, and language abilities. Unnatural features generally first appear in the brain tissue that covers the frontal and temporal lobes, and then little by little advance to different fields of the neocortex at rates that change greatly among people. Alzheimer's disease is corporate with the collection of indissoluble shapes of amyloid-β (Aβ) in plaques in extracellular spaces [23].

Plenty of the features of Alzheimer's disease are frequently classified into three stages mild, moderate and severe (Figures 4-5-6). It is substantial to remember that not all of these characteristics will be available in every individual and that they may occur at diverse stages for some people.

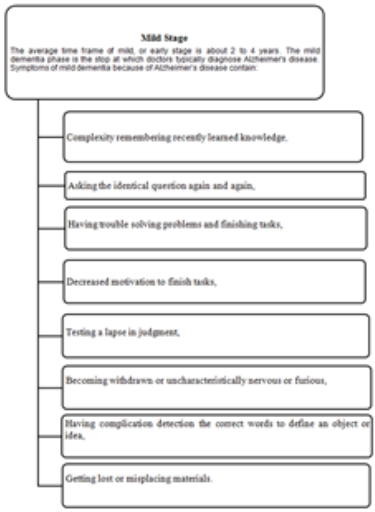

Figure 4. *Mild Stage of Alzheimer's disease [24]*

Figure 5. *Moderate Stage of Alzheimer's disease [25-29]*

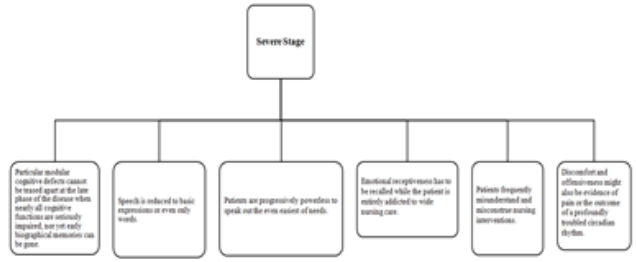

Figure 6. *Severe Stage of Alzheimer's disease [30]*

The start-up medication of AD are Acetylcholinesterase inhibitors as they help with slight healing in cognitive function, behaviour and daily life activities. Though no clinical suitability has been found to the extent of their positive effects, some of the side effects of these medications are cardiac arrhythmias, dizziness, diarrhea, nausea, confusion and vomiting.

Memantine, a generally overlooked N-methyl-D-aspartate receptor antagonist, can positively affect cognition and attitude of patients with AD when used short-term. It may also be used together with acetylcholinesterase inhibitors.

The benefit of selegiline, testosterone, and ginkgo for the therapy of AD is disputed. Likewise, there is no significant proof on the useful effects of estrogen, vitamin E, or nonsteroidal anti-inflammatory medicine treatment. Attempts on reducing amyloid plaque charge by shifting amyloid metabolism such as Immunotherapy for the clearing of β-amyloid are explored [31].

3. MICRORNAs and NDD Association

MicroRNAs (miRNAs) are important epigenetic regulators of diverse cellular operations. They include evolutionarily preserved, noncoding 15–22 nucleotide RNA molecules that construct gene expression at the translation grade. miRNAs have a various range of functions including mRNA degradation and translational repression, cell proliferation, differentiation, growth control, homeostasis, and apoptosis [32]. miRNAs, which are also known to be extremely expressed in the human brain, serve like transcription factors to direct gene expression. In spite of ~70 % of the given miRNAs are expressed in our brain, solely several of them are brain-specific and brain-enriched [33].

Since miRNA's are important for the tissue and cell type-specific enrichment within the nervous system throughout neurodevelopmental stages, a broad range of research has been done in the area of modifications of miRNA during pathologic circumstances like heart diseases, cancer, homeostasis, and neurodegeneration [34-39].

According to recent research, 2578 mature miRNAs are established in human beings [40]. A miRNA molecule is linked to the identification location on varied mRNAs, later organizing their expression [41]. That's why, miRNA–mRNA mutual effects are able to alter the expression of

hundreds of genes, thus regulating the appropriate cellular and molecular networks. [42].

Research has shown that miRNAs are an appropriate tool for the identification, prognosis, and treatment of some diseases based on their functional roles in many distinct biological pathways. Not all miRNAs have a functional biological purpose. Cell-based screening programs making usage of appropriate platforms like differentiated neurons, primary cell cultures, induced pluripotent stem cells, and cell lines can make the recognition of promising nominees easy. miRNA-based therapeutics shelter excellent potency due to their skill to silence poly genes at the same time. Owing to the complication of the pathogenic operations elementary to the progress of neuropsychiatric diseases like ASDs, miRNAs might be the best appropriated for medicinal aiming of diverse mRNAs [43].

In general, there are 2 approaches to emerging miRNA-based therapeutics, including miRNA antagonists and miRNA mimics.

miRNA antagonists are formed to restrict endogenous miRNAs that show a gain-of-function in unwell tissues. This oncoming is conceptually equivalent to other inhibitory therapeutics that goal an individual gene yield like minor molecule inhibitors and short interfering RNAs (siRNAs). miRNA mimics are used to renovation a loss of function. This approach, also known as miRNA replacement therapy, aims to reintroduce miRNAs normally expressed in healthy cells into diseased cells [44].

Dysregulation of miRNA's are linked to diverse neurological diseases. Research has shown that miRNA processing machines, as well as the precursor and mature miRNAs, might become disordered during the advancement of any neurological disease [45]. Some

neuropsychiatric disorders in which aberrant expression of miRNAs are observed are; Schizophrenia, Autism, Bipolar Disorder, Depression, Anxiety, and Addiction. These unusual expressions were also observed in the following neurodegenerative disorders: Amyotrophic Lateral Sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease [46].

3.1 microRNA's and Autism

Autism is identified by defects in communal interaction and communication, and by iterative and routine behaviour's. It is of utmost importance to find prognostic biomarkers which could catalogue for autism before the initiation of signs. microRNAs have nowadays emerged as significant epigenetic regulators of diverse cellular durations with the inclusion of neurodevelopmental. miRNAs are seen as possible targets in developing new therapeutic tactics for autism. [47].

In a study done by Vasu et.al (2014) expression change in 13 miRNAs was observed in ASD subjects. The research group found hsa-miR-181b-5p and hsa-miR-328 as peripheral biomarkers reflecting the miRNA expression profile of autistic subjects.

miRNAs are also able to affect gene silencing over translational repression or mRNA corruption [48]. This mRNA disrupt might modify a few downstream pathways and induce several remarkable effects [49]. Five miRNAs (miR-130a-3p, miR-19b-3p, miR-320a, miR181b-5p, and miR-572) showed significant association with the pathogenesis of ASD [50 - 52].

Some central genes and miRNAs associated with Autism are shown in Table 1.

Table 1. *Central Genes of Autism and Several Detected miRNAs from Autism Related Genes [53-61]*

Central Genes of Autism	Detected miRNAs from the Central Genes of Autism
HSPA1B	miR-15/16
MYO5A	miR-25
RUNX3	miR-130b
EHD4	miR-515-3p
ARRB1	miR-326
CTBP1	miR-132
USP36	miR-151a-3p,miR-342-5p,miR-615-3p,miR-98-5p
SPON2	miR-181a-3p

3.2 microRNA's and Alzheimer's Disease

Wang-Xia W. et al. (2008) used miRNA expression microarrays on RNA taken from human brain tissue. They recognized miR-107 grades reduced remarkably in patients with the first phases of Alzheimer pathology, BACE1 mRNA grades tended to increase as miR-107 levels reduced in the improvement of AD [62]. Kumar and Reddy (2018) defined MicroRNA-455-3p as a Potential Biomarker for Alzheimer's disease [63]. Also Martinez and Peplow (2019) discussed MicroRNAs as diagnostic and therapeutic tools for Alzheimer's disease, their advances as well as limitations [64]. Some central genes and miRNAs are shown in Table2.

Table 2. *Central Genes of Alzheimer's disease and Detected miRNAs [65-73]*

Central Genes of Alzheimer's Disease	Detected miRNAs from the Central Genes of Alzheimer's Disease
APP	miR-106b, -20a, -17, -106b, -106a, -155, -101, -16, -147, -153, -323-3p, -644, -655
GSK3B	miR-346
CLSTN1	miR-1908-5p
BPTF	miR-145
CASP3	miR-224
CASP2	miR-383
CDK5R1	miR-103 ,miR-107
APBA1	miR-30a

CONCLUSION

Neurodevelopmental disorders are defects associated mainly with the functioning of the neurological system and brain. Most neurodevelopmental disorders have complicated and various contributors rather than any particular obvious cause. Schizophrenia, autism spectrum disorders, epilepsy, mental delay and communication disorders are some examples of Neurodevelopmental diseases. These disorders are a presumably consequence from a combination of genetic, biological, psychosocial and environmental risk factors.

MicroRNAs (miRNAs) are important epigenetic regulators of diverse cellular operations. Research has shown that miRNAs are an appropriate tool for the identification, prognosis, and treatment of some diseases based on their functional roles in many distinct biological pathways.

The number of people with Alzheimer's disease and autism spectrum disorder is increasing. Many studies have been conducted to investigate whether Alzheimer's disease and autism spectrum disorder are associated with miRNA. This makes miRNAs a source of hope for the treatment of these types of diseases.

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