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PROF. DR. CEM EVEREKLIOĞLU
DR. MEHMET ERTEN

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Editörs

Prof. Dr. Cem EVEREKLİOĞLU[1]

Dr. Mehmet ERTEN

1 Erciyes Üniversitesi Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Kayseri, Türkiye, everekliogl u@erciyes.edu.tr

gece kitaplığı

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CHAPTER 1

CARE AND SPIRITUAL SOCIAL WORK ON THE AXIS OF SPIRITUALITY

Dr. Sema SAĞLIK[1], Şeyda DEMİR[2]

1 Dr. Öğrt. Gör., Sosyal Hizmet Bölümü, Esenyurt Üniversitesi
E-mail: sema.saglik@meb.gov.tr
2 Yalova Üniversitesi, Sosyal Hizmet bölümü, Sosyal Hizmet Anabilimdalı
E-mail: seydademir44@gmail.com

Introduction

What makes a person a social and cultural being is the environment in which s/he lives. In a totality, a human being is a being that constantly interacts with all dimensions. These interactions are different for each field as they are so for each individual. Every person has features that cover many areas such as the cultural structure, language and communication styles, health, beliefs and practices, and traditions in which they live. For this reason, when evaluating people; cultural, psychological, biological, social and spiritual dimensions should be considered as a whole. When the literature is examined, there is no consensus on the definition of the spiritual dimension. It comes from the Latin word "spiritus", which deals with the quality of life in a broad concept and means "to breathe" and "to be alive". It is to feel life in a broader sense (Ewen, 2004; Gürol, 2004).

Spirituality can be defined as "the general human experience of developing a sense of meaning, purpose, and morality," while religion can be defined as a more formally institutionalized belief system and practices set forth accordingly (Zastrow, 2013: 152). Religion can be defined as a system of thoughts and actions that are shared within a group and that provide a ground and an object of worship that will enable group members to find a direction (Fromm, 2015: 31). Spirituality is defined as a human need to create meaning and order in a chaotic existence, and is not necessarily related to organized religion (Cascio, 1998: 524). In other words, a non-religious spirituality is possible. Man's contemplation and desire for self-discovery also correspond to a spiritual experience (Akbaş, 2014: 99).

Spirituality is individual and private. Spirituality provides the individual and his family with the application of certain feelings in the event of illness or difficult situations that can result in death. Unexpected changes in health often cause reflections in patients and their families in the form of questioning the meaning and purpose of life, and hope in illness. Reflections appear as spiritual beliefs and become one of the coping mechanisms of the individual in cases of suffering (Callister, 2004). These beliefs become more important to individuals when they lose health, helping them to accept their illness and plan for the future. Their beliefs guide their behaviour by influencing beliefs, thoughts, views, teachings and lifestyles of individuals. In this case, the purpose of applying spiritual care to the individual is not only to help for his physical well-being; At the same time, it should be to ensure the balance of body, mind and spirit.(….eksik cümlenin yeri burası). Need for care is a neutral concept independent of the age of the individual and is explained by situations that deviate more or less from what is considered normal. This situation can make people in need of care uneasy, lead them to despair and shake them spiritually, as it

sometimes means that a person loses his or her closest relatives, distances oneself from loved ones, is pushed into loneliness and becomes constantly dependent on others. For these reasons, there are convergence points of spirituality and social work in the social work discipline. In this regard, many social workers, educators and students underlined the necessity of regaining the lost spirit with the rejection and neglect of spirituality in the field of social work (Canda, 1999).

McKernan's (2005) study suggests that spirituality and social work converge on three important factors; "the first factor is a change in the bond with spirituality; the second factor is humanity's need for a new window, and the third factor is the desire of social work to build a bridge between its roots, that is, between various religions and philanthropic work, and spirituality". In addition to McKernan, Akbaş also expalains it with "the consideration of spirituality in the context of social work; this concept's being moved away from being seen as a certain way of believing that only a certain group has, as well as the fact that scientific progress and control is helpless and inadequate in the face of global terrorism, environmental crises, wars, massacres and global poverty, and therefore humanity needs a new window."

Spiritually social work develops spiritual indoctrination and therapy methods for people who do not feel well, who are suffering from hopelessness and spiritual diseases, who are perverted in belief and thought, to regain their old health. Spiritual care, which can contribute to solving problems and facilitating social adaptation, should contribute to better determining life goals and responsibilities with the information it provides on the meaning and value of life. National and moral values of social work activities should be applied to the individual. In other words, the concept of social work, especially the spirit; The basic philosophy of spiritual social work should be to shape it by turning to spiritual qualities and resources such as mind, will, heart and conscience.

With its spiritual dimension, social work is "individual holistic services carried out with the aim of strengthening the social functionality and spirituality of the society, groups, individual, increasing their commitment to life, being at peace with their inner world, and eliminating their spiritual deviations and fears" (Ewen, 2004). In order for the individual to be in a state of well-being, it is necessary to evaluate his spiritual health as well as his physical, social and spiritual health. Spiritual care is the basic part of holistic care and considering the integrity of the human being, it can be said that it is healthy when all its dimensions are balanced.

Spiritual practices are important in social work practices in Turkey as well as spiritual and religious perspectives in social work practices in many

countries. “Given that Turkey has more than one ethnic origin and spiritual differences, social workers are expected to show cultural sensitivity and to be able to realize the cultural identities that the clients can reveal in the process” (Apak, 2017: 66).

In this context, the aim of the article is to introduce a spiritual care model that will be applied to the needy, disabled, elderly and chronic patients by meeting their spiritual needs and to bring new initiatives to social and spiritual care practices in accordance with our national culture. In addition, it is to clarify the points to be considered for effective implementation and to develop suggestions for spiritual social work practices in Turkey.

For this reason, in the study, firstly, it was tried to examine whether the spiritual values of the individual have a relationship with social services, the relationship between the spiritual values of social services and their contribution to the individual from the perspective of spiritual care. Then, the spiritual care model and strategies, the skills required to provide spiritual care, and the points to be considered in practice were clarified; a spiritually social work approach was defined and suggestions were made.

Conceptual Framework of Spirituality

Spirituality in the Western style does not necessarily have to have a religious element, but religious feelings do not need to be considered outside of spirituality. In this context, the ICF defines it as “participating in religious or spiritual activities, arrangements and practices in order to connect with spiritual values and divine powers, find meaning and self-realization” where deemed necessary. We can include religious and spiritual activities such as praying, listening to hymns, going to the mosque, indulging in spiritual thought (ICF, 1930). Spirituality, which includes all kinds of thoughts, is a strong faith based on surrender to the Creator, the hope of finding the truth, and a divine journey in its inner world.

It is important to know the nature of spirituality and to put it on spiritual foundations, in order for the positive effects of empowerment, change and development of service recipients with interventions sensitive to spirituality proven by many researches (Limb and Hodge, 2008; Hodge, 2006; Nielsen and Ridley, 2000; Hawkins, Tan and Türk, 1999; Keskin, Bilge and Babacan, 2005), and for its efficient and effective application in Turkey.

The Nature of Spirituality

Spiritual and psychosocial needs are more social and complex than physical needs, and they are also difficult to measure. For this reason, the physical needs of the individual, which can be measured more clearly and easily in health care, are handled first, while their spiritual needs can be overlooked. However, it is very important to define the spiritual needs

of the individual and to provide the necessary care. There is a need for spiritual care services that aim to alleviate the spiritual burden of those in need of care and to ensure their peace. Spiritual needs are those that will reduce the spiritual deprivation of the individual and support their spiritual strength. They are the factor or factors necessary for an individual to maintain a dynamic relationship with superior power. Only physical needs, which are clear and easily measurable in the care of the individual, are considered primarily because they are abstract and complex compared to physical needs, while spiritual needs can be overlooked (Aydın, 2003). For this, first of all, it should be known what spirituality is and how it is expressed by individuals. Many definitions in today's literature both help define spirituality and reveal the differences between spiritual needs (Ergül and Bayık, 2004).

According to Ross (1994), Simsen (1985) defines spirituality as "the sum of all the internal resources of the individual with which he is related beyond matter and their basic meanings". In the dictionary of the Turkish Language Association, spirituality is defined as "immaterial spiritual things (invisible, intuitable, abstract, spiritual)" (TDK, 2003).

As Oldnall (1996) said, spirituality is the power that helps the individual; the spirit he feels inside; It is the beliefs and values that give meaning to human life. Therefore, spiritual care is a universal model that respects the spiritual values of all people in need of care living in the cultural geography. As the definitions suggest, spirituality provides support, hope, and involves finding a meaning, purpose, and way out of life. During life-changing events, people often turn to spirituality for comfort, hope, and relief from stress. Many researchers consider spirituality as an important part of being human and in relation to all other human dimensions. It can be an important part of coping during a crisis of illness and positively influence someone's response. Spirituality can help an individual define "the self" in times of illness. A person's personal relationship with someone they perceive as a higher power or with God can provide support and be a source of hope for a positive outcome. The content of all these definitions clearly reveals their purpose and what they will do in the spiritual care that they give to the individual (Hutchinson, 1997).

The spiritual aspect of the individual is as important as the physical, emotional and social aspects. There are many research results that indicate that individuals with a developed spiritual aspect are healthier physically, emotionally and socially. These individuals may have high hope levels and low depression and isolation tendencies. They can cope with stress better, and as a result, they can improve the quality of life. However, today, the social work discipline ignores this aspect of the individual or has a great deficiency in providing care in this direction.The sum of the socio-cultural

values adopted by each nation depending on its internal dynamics can appear as an external reflection of spiritual values with its social dimension. Spirituality, which is sometimes thought of as a religious dimension, is actually a separate phenomenon. It is defined as the supreme power of belief, the power to create, the divine, or the infinite power of energy. For example, for a person who believes in Allah, Allah is considered to be the one who gives him strength, the holy one, "Allah" or the "Higher Power". Religion, on the other hand, is the organizational form of the worship system and is concerned with core beliefs, ceremonies, and practices (Öz, 2003). Spirituality is present in all individuals and can manifest itself as an invisible God, absolute truth, or inner peace and strength arising from any individual value that one qualifies as superior. The spiritual dimension evokes emotions that indicate the presence of love, hope, faith, trust, inspiration and creates the reason and meaning of existence. When the individual is faced with emotional stress, physical illness or death, he focuses especially on the spiritual dimension.

Assisting an individual in preserving, maintaining or attaining all dimensions of their existence are the foundations of spiritual care. These elements are a universal phenomenon according to Existentialism, that is, they are present in all of us (Macquarrite, 1972). Therefore, we are all capable of realizing this unique potential. This potential encourages us to find meaning and purpose in life. So existentialism argues that even non-believers seek inner peace. Therefore, it is seen that human beings, whether religious or non-believers, have spiritual needs.

According to Hardy (1979), religious awareness or spirituality is unique to the human species and has found value because it has biological survival value. Hay (1994) argues that spirituality is a perceptual experience rather than a theoretical belief. Hardy developed the hypothesis that such an experience is perfectly natural, while Hay drew on psychology, animal behavior, psychic research, and anthropology. According to Hay's research, people often become more spiritually aware at the slightest emotional stress, physical illness, or crisis of any kind. However, this often remains a personal secret; because it is feared that others will make fun of this situation and make the person look stupid (Hay,1987).

All of these authors' definitions are that "spirituality is a broad concept that can be expressed in both religious and non-religious orientation; therefore, there is a consensus that individuals who are deists, atheists or who have adopted any religious belief have their own unique spirituality.

Spiritual Foundations

Some writers, writing from a Christian perspective, claim that active spiritual belief and spiritual practices are a source of hope in their own

right (Bradshaw 1994; Carson 1989; Shelley and Fish, 1998). However, some believers may take part in activities such as praying, worshipping, listening to hymns or watching television, listening to religious programs on the radio, joining religious groups. The positive relationship between those who take part in these activities and the person who will provide the spiritual care will help the patient to express his/her ideas, fears, and concerns, so that s/he will be able to evaluate his/her own spirituality in need of care from new perspectives. One will be able to find inner peace and gain strength from his/her beliefs.

Learning Process

Communication and counseling skills in spiritual caregivers can be improved with 'experimental' (Harrison and Burnard 1993, Burnard 1990, Knowles 1980) and student-centered learning (Rogers 1984) techniques. A spiritual care program can be created by addressing issues such as professional competence, social psychology, disability, need for care and care organization. The Islamic University of Rotterdam opened the "Islamic Spiritual Care" program on April 25, 2011 to teach the characteristics of spiritual care in both broad and specific sense by approaching the issues through specific Islamic values. As a European University, the Islamic University provides education based on the religion of Islam in the Netherlands and breaks new ground. Scientific methods and traditions accepted in the Islamic world have an important place in the curriculum of the Islamic University, which aims to teach Islamic sciences at an academic level in Dutch society.

Spiritual Care

If we see it as a professional and ethical responsibility for social workers to provide spiritual care, we see it as the responsibility of the education of social workers to define the spirituality of the person and the issues of providing spiritual care. In fact, education begins with the feeling of spirituality. Seyyar explained the integration of the concepts of spirituality and spiritual care into the social work education program (Seyyar, 2010). Seyyar (2010), starting from the thesis that "the philosophy on which spiritual social services are based is human nature", compared the natural human model with the philosophy of positive social services, and states that "the natural human model is based on a spiritual basis, while the positive social work philosophy is based only on reason and ignores spiritual elements. argued that in this respect, its impact was more limited than that of spiritual social work.

Şirin (2014: 64-65) argues that "there are three different approaches to religious guidance/spiritual counseling/spiritual support: The first is the approach based on the holy book. This group is based on using the holy

book and the verses in it as a counseling tool. The second group is those who use the data of psychology along with the holy book. The third group is the group that believes that counseling should only act in accordance with psychological data in solving emotional and mental problems. Considering these approaches, it is necessary not to ignore religious, moral and mystical issues while considering the principles of psychology for "spiritual care" and the mental and emotional characteristics of the client. Indeed, the results of Dr. Jeff Levin, after examining more than 200 studies on faith and health in his book "God, Faith, and Health", support this view (p.86). According to the findings of his studies;

• Generally, religious people lead healthier lives.

• People who attend mosque, church or synagogue are more social in society. Being with other people gives a person spiritual strength. Living in social solidarity with the community is always good for health.

• Worship and mass prayers activate positive feelings and thought. Positive feelings, on the other hand, contribute to positive psychological changes and positive health improvements.

• Optimism and hope have curative effects on diseases.

Another study, Koenig et al., (2000-24-74) in the "Religion and Health Handbook", analyzed the common results of 1200 studies and came to the following conclusion: Statistically, there is a positive relationship between physical health and individual belief". In short, using the spiritual power in addition to the worldly interventions in the interventions applied to the client makes them feel their life satisfaction at a higher level. The client, who is in a spiritual state, can regain his health in a shorter time with spiritual approaches. The following verse in the Qur'an is a clear proof of this: "They will put their trust in no one else, but only in Allah." (Abraham, 14/12). In addition, the following meaningful words of İbrahim Hakkı from Erzurum are of the quality that can help all patients undergoing treatment to relax spiritually: 'You put your trust in God, Surrender and find comfort, Be content with all your work, Let's see what happens, Mevla, whatever happens, does well'. The positive effects of "contemplation, trust and gratitude" confirm that there is a positive correlation between belief and health.

Aydın (2021: 279) states in Harrington's (2021: 275-307) article that this issue consists of four individual claims:

- Going to church increases life expectancy and resistance to disease.
- Spiritual practices (such as meditation) reduce stress and strengthen health.

- Faith in God facilitates the healing of serious illnesses.
- Praying for another can change the outcome of the illness. It is seen that a holistic approach is needed in the interventions. In this respect, spirituall social work overlaps with a biopsychosocial and spiritual approach that emphasizes a holistic view.

In this context, it is considered appropriate to evaluate spiritual care from the perspective of the client's powers.

In spiritually social work practices, Ross (1996) recommends teaching spiritual care and the ASSET model. But his question is, "Can spiritual care be taught? Or is it more defined by the personal characteristics of the social worker?" is in the form.

Ross (1996) argues that learning these concepts rather than teaching them academically, in other words, making them aware is a better model, while McSherry (2000) argues that learning the concepts of spirituality and spiritual care is complex and different concepts, therefore, by teaching them with traditional education techniques, he proposes to increase the awareness of the student about the subject in the practice environment. Narayanasamy (1999) created a spiritual care education model that will provide intercultural care with the ACCESS (Assessment, Communication, Cultural Negotiation and Compromise, Empathy and Respect, Sensitivity and Security) model (taking action in spirituality and spiritual care education).

The educational content of the ACCESS model consists of understanding spirituality in its broad dimensions, developing self-awareness on the subject, diagnosis, planning, implementation and evaluation within the scope of the spiritual dimension of spiritual care. It is aimed to provide this care to the individual in a desired manner as a result of gaining awareness in the student as a result of trying this educational content and gaining it with applied teaching techniques, and gaining appropriate knowledge and skills (communication skills, establishing a relationship of trust, giving hope, supporting). This model provides a useful framework for the field of health applying the practice of intercultural care. Due to the positive application results in the field of health, this model is considered appropriate in other disciplines.

The main point on which the authors with different views agree is that in order to be able to give spiritual care, it is necessary to have enough information about the dimensions of spirituality and to be aware of their own spiritual world, values, beliefs. The fact that the person who will give spiritual care does not have this competence will create difficulties in identifying the spiritual needs of the person he cares for. The prevailing

view on this issue is that he can gain the necessary knowledge and skills by understanding the basic theories of the concept of spirituality and the principles of spiritual care through case studies. In this sense, it is very difficult to evaluate his awareness of spirituality and his personal development. Evaluation can be made as a result of the attitudes and initiatives of the student in the face of the situations related to these issues in the practice environment (Collister, 2004).

Spiritual Care Strategies

Interpersonal connection: meaningful sharing with relatives and others means interpersonal connection. E.g; harmony and support in the family gives hope and strength, which are the basic requirements of spirituality.

Carefreeness: It appears in features such as pleasure, fun and joy, and these can be expressed very easily, either verbally or physically. In spiritual care, one can be encouraged to be carefree. This can be like therapy as it provides a means of interpersonal communication. Thus, the person finds a way to cope with the deterioration of bodily functions and emotional turmoil. The person giving the spiritual care can highlight the personal characteristics of the person in need of care, such as determination, courage or inner peace. Supporting the caregiver in her search for peace and tranquility helps her find inner peace. A few verses that will help to find inner peace are as follows: In verse 48 of the chapter of Shura, it is clearly stated that the misfortune that befalls man is caused by "the sin he has committed with his own hands": "When we make man taste a blessing from Us, he is relieved by it. But if evil befalls a man because of what his own hands have earned, then he is an ungrateful person who forgets all his blessings". It should be clearly understood from this verse that; The Creator exposes them to misfortunes, troubles, torment and destruction because of their own denial, polytheism, hypocrisy, rebellion and mistakes. For example, if a person goes to a balcony that will be demolished and the balcony collapses, if he falls and breaks his leg, whose fault is it? Of course, it is the one who goes to the balcony to be demolished. This is an appreciation. However, that person caused this with his wrong move. He will pay for the mistake by breaking his leg. So he will be punished for his mistake. "Whatever misfortune befalls you is because of what you have done with your own hands." (Shura, 30). If a person acts contrary to these orders, does bad things and does not take the necessary precautions, of course, what happens to him will be because of his own mistakes. He will pay for these mistakes himself. This world is a world of testing. Man is under test throughout his life. The duty of man is to come out of this test successfully. For this reason, one should take lessons from events, calamities and disability. Troubles are the words to wake up the heedless person, "One misfortune is better than a thousand advices." (Karagöz,

1996). Of the attainable goals, personal goals are a powerful factor in the search for meaning and keep hope alive. Helping a person achieve their goals and clarify their thoughts means invigorating a sense of hope.

Skills Necessary for Giving Spiritual Care

The following skills are required in spiritual care practices: "Communication Skills, Building Confidence, Giving Hope, Belief and Confidence in Other People and Superior Power within Oneself".

Communication Skills: The most basic requirement for spiritual care is to be able to listen without judgment. There are times when the person in need of care just wants to talk to get rid of the burden of their thoughts and feelings. The ideal person to listen to him should be the one who gives spiritual care. Therefore, it may be necessary for the person who will give spiritual care to accept the person in need of care unconditionally and to create the right environment for him to express his spiritual feelings and thoughts.

Building Confidence: In addition to communication skills, the person who will give spiritual care should also have adopted trust-building strategies. This is achieved by showing genuine interest and concern for the other person. Keeping promises, protecting confidentiality and trying to meet their needs give the patient confidence.

Giving Hope: Hope is an important part of spirituality; however, it is not something we can easily give one another. Efforts should be made only to raise the hopes of those in need of care. The ideal person to do this is the person who gives spiritual care. (Naraya…1994) The needy can be encouraged to talk about their fears. It can bring back memories of good times. It can be reminded of the moments in life when he got what he wanted, overcame his hopelessness, and overcame failures. According to Hert (1990), hope cultivation strategies can be used as a part of spiritual care. Herth (1990: 1255) also mentions that people who will give spiritual care can participate in group work to give hope to the individual.

Belief and Confidence in Other People and in the Supreme Power Within Oneself: Although man is very strong by nature, it is certain that he always needs a support in his inner world. We sometimes see this information as a revelation, sometimes as a dream, and sometimes as a suggestion. We call each of these spirituality.

Spiritual Beliefs and Values

Spiritual Belief: If the individual with spiritual beliefs is a whole with physical, mental, emotional, socio-cultural and spiritual dimensions, it is an inevitable fact that the dimensions that make up this whole should

be considered separately from each other. Studies have shown that the spiritual dimension has a clear effect on health, well-being, and quality of life (Coyle 2002; Wright 2002; Ergül and Bayık 2004; Govier 2000). Spiritual beliefs and values care about sensitivity to moral, humanistic and existential issues, regardless of any doctrine. In addition, people who do not have strong religious beliefs also have spiritual dimensions, spiritual values and beliefs are a phenomenon far beyond belief in a being or power, health, sin, life after death and responsibility towards others, devotion, compassion, empathy, belief, kinship etc. It is known that it includes beliefs about the issues (Çetinkaya et al. 2007; Kostok 2007).

Spiritual Values: Reflected in their personal and social dimensions, they also contribute to social capital as they enable people to live in unity. The external social and spiritual benefits of people who can easily live their spiritual values in stability and security will also be high. People with high spirituality are patient, determined and decisive. People who are spiritually, who struggle to overcome all kinds of obstacles that life presents to them, and who accept to live with the obstacles even if it is not possible, will be able to be at peace with both themselves and the society with their open-hearted, broad-minded and harmonious characteristics.

Spiritual Bond: Man is not completely disconnected from the spiritual realms, because he is also connected to the spiritual bond by nature. Spiritual bond has a social and a divine dimension. The social dimension is the connection and interest established in the heart. The divine dimension is the spiritual connection, the awareness of the ways connected with the Creator and his works, or the spiritual closeness of a person who is spiritually awake (Seyyar, 2008). This spiritual bond not only keeps the person away from all kinds of evil, but also makes it possible to adhere strictly to their worship. As a result of coming together with a harmonious spiritual frequency and loving for the sake of Allah, their emotional sensitivity increases. Spiritual social services and spiritual care services accept the function of the spiritual bond in the happiness of those around them and their success in social life, and help people in this direction with internal cleansing and spiritual support services. In this support process, the person's attitudes and behaviors will be aimed at gaining Allah's approval and complying with the moral conditions brought by the society.

Spiritual Development: Spiritual development ensures that our spiritual spirit is enriched and that its spiritual needs are met through faith and worship. In other words, in the process of values (character) education, it is to renew itself in the spiritual field and to reach the consciousness of having a personality beyond being an individual. Spiritual social services and spiritual care practices also take the person on a journey to

real happiness and support them with psychosocial methods and spiritual guidance services.

Spiritual Needs: Spiritual needs are much more complex than physical needs. However, defining the spiritual needs of the person and providing the care that will meet this need is only possible with spiritual care services. Spiritual needs are important to all people; because they satisfy these needs through human relations. According to Renz (2003), the requirements related to spirituality are divided into 3: belief and trust in the Creator; attachment to life with hope; The meaning of the concepts of suffering and death is the purpose and the need to find power (as cited in Seyyar, 2007).

The Impact of Spirituality on One's Happiness and Health

Scientific studies conducted in the Western world have determined the positive effects of spirituality on the ability to increase living standards, overcome disease, and live with diseases. On the other hand, it has been proven that there is a 25% decrease in the prevention of substance addiction, reducing or eliminating pain, removing obstacles and strengthening morale (Başbakkal, 2005). For research on spirituality in the Western world, 70 university-affiliated centers in the United States explore spirituality and its effects on health, personal development, and social life.

As a result, Harold G. König (2012: 169-183) makes the following determination: "Although research reveals the connection between belief and physical well-being, the evidence showing the benefits of spirituality for psychological and mental health is stronger" (Camiü-s-Sagir, 2002).). However, since the studies were carried out on subjects belonging to the Christian and Jewish religions, it is clear that devotion to the Creator will also be valid for Muslims who live the religion of Islam sincerely.

Switzerland, St. Gallen, Head of Psycho-Ontology, Music and Psycho-therapeutic Monika Renz (2003) conducted a study on religious patients suffering from cancer or similar serious diseases. It has been observed that more than half of the patients with high spirituality have less physical pain and are quite at peace with diseases. Monika Renz has documented these interesting results in her book "The Borderline Experience God: Spiritual Experiences in Pain and Illness" (Renz, 2003). As a result of a study consisting of 126 thousand subjects, which on the connection between adherence to religious activities and average lifespan, it was revealed that a lifetime spent with religious activities has a life-prolonging effect (McCullouhg, Hoyt, Larson, Koenig, Thoresen, 2000). People who attend mosque, church, synagogue are more socialized, and socialization gives the person spiritual strength. Living in social solidarity with the community is always good for health.

Spiritual Social Work

Social work is the whole of professional work carried out in order to strengthen the social functionality of individuals, families, groups and societies in general. Social work acts as a bridge between the individual and his/her environment. It is a profession that evaluates and deals with the problems that affect social functionalities and different living situations that arise as a result of interactions, and has the authority to intervene.

Due to its holistic approach, the social work profession cannot handle the problem in isolation from the problem owner. It is necessary to focus on the problem owner, just like the problem, in the stages of investigation, diagnosis, planning, implementation and evaluation because it is the main task of social work to try to eliminate the conditions that caused the problem and to show the problem owner the ways to solve the problem. In this case, the emerging conditions and the owner of the problem should be the focus of social work as well as the problem itself (Kongar, 2007).

Spiritual work in social services or social services in the spiritual journey is the implementation of social work activities in a manner appropriate to national and spiritual values, adhering to the spiritual human model. Spiritual social services, which emphasize social and spiritual education aimed at raising moral individuals, realize the understanding of social work by turning to resources such as the heart, conscience and mind in the individual. A person who has a holistic view with his spiritual dimension will say, “How beautifully created!” instead of saying,“How beautiful!” and so he delivers the truth. Instead of saying “Do all troubles find me!”, “Every problem we see contains a good.” should be said. Therefore, since providing inner peace in the individual and social peace in the society will also establish justice, it is necessary to bring the axis of spirituality to social work practices. Otherwise, it will push the society into a spiritual vacuum, the cases will tend to deviate from the bad and the individual will move away from the society.

Spirituality, as Tarhan (2017) said; “It is the background of matter, its dimension of meaning. Abstract concepts add meaning to concrete perceptions. We create everything we know, every body, with abstract concepts. Abstract and symbolic thought reveals the true nature of everything.” However, it should be considered normal that spirituality has different connotations in everyone’s minds. “Therefore, the place where the individual captures the meaning and purpose of life is his spiritual realm. This area can also be a subjective and latent relationship established with the believed superior power or a relationship that the individual attributes to nature, art, music, family, social environment and values and beliefs (Tuncay, 2007).

Legal Basis of Spiritual Social Services

Spiritual social work reflects the fact that their professional activity is the most subordinate right of people, not just out of need. Every situation that falls within the field of interest of the spiritual social work profession has the quality of the concept of rights. In the Preamble of the Constitution of the Republic of Turkey (1982), it makes a statement about the development of people not only materially, but also spiritually. The statement that "every Turkish citizen has the right and authority to live a dignified life in the national culture, civilization and legal order and to develop their material and spiritual existence in this direction, by benefiting from the fundamental rights and freedoms in this Constitution, in accordance with the requirements of equality and social justice," clearly states that people are in a spiritual development. In the section "Basic Purposes and Duties of the State", a concrete explanation is made for the spiritual development of individuals. The aims and duties of the state are to protect the independence and integrity of the Turkish nation, the indivisibility of the country, the Republic and democracy, to ensure the welfare, peace and happiness of individuals and society, to remove the social barriers that limit the fundamental rights and freedoms of the individual in a way that is incompatible with the social state of law and the principles of justice, to try to create the necessary conditions for the development of its material and spiritual existence (TC Constitution, 1982). For this reason, it is a constitutional duty to prepare the conditions for the spiritual development of people, to determine and implement appropriate spiritual social service programs. In other words, the social state is obliged to take the necessary measures for its citizens to live in spiritual peace.

In the 21st century, the reflections of science on the individual and social life of people are increasing day by day. The science that will be most affected by this change in science is undoubtedly the social sciences. The function of social sciences, explaining social events in the cause and effect relationship and reaching general judgments have lost their validity today. There is no longer a single reality or a single truth regarding events and phenomena in the social field. There are multiple realities, different and various perceptions (Yıldırım & Şimşek, 2008).

The concept of social services is defined in the Law No. 2828 on the Social Services and Child Protection Agency as follows: "a systematic and programmed set of services aimed at to help individuals and families meet their material, moral and social deprivations arising from their own constitution and environmental conditions or beyond their control; to help meet their needs; to prevent and solve social problems, and to improve and upgrade living standards of them".

As it can be understood from the definition, the emphasized spiritual deprivation emphasizes an important need when viewed from the perspective of needy help. Poor families trying to cope with social risks, especially children in need of protection, the disabled in need of care, the elderly, chronic patients, women who have been subjected to violence, need moral support more. The positive relationship between spirituality and coping was investigated on 29 young people, 23 men, 6 women, who were later disabled. According to this research, it was thought that the opinion about disability among disabled youth was related to God. Their injuries had a religious content and were considered as a part of God's will (Kula, 2005). Individuals exposed to social risks need more moral support. Spiritual social work practitioners should provide spiritual counseling and guidance services to the individual, family and society, and provide spiritual development to support the problems of the individual (Şeker, 2008).

Discussion, Conclusion and Recommendations

The most important pillar of creating a clean society is probably morality, because man does not only have material elements, and since man is a being with a spiritual dimension, we cannot ignore the spiritual dimension in human relations. This spiritual dimension of man is composed of belief and morality. If this spiritual dimension of man is ignored, it is inevitable that we will encounter problems such as murder, corruption, etc. Therefore, there is a need for spiritually social services to overcome the negativities experienced recently. The blood feuds, murders, suicide cases, which tend to increase gradually in our country, show that social issues are getting deeper. Such cases attract much more attention in our country, and the sociological and psychological point of view often remains in the background. Although social events occur within the framework of certain reasons, they may differ according to the understanding and value systems of societies.

The point that many thinkers agree on is that each country should build social sciences according to its own socio-cultural characteristics. We can directly take and use science and technology sciences, but we have to build social sciences in the light of our own national and moral values. Unfortunately, this light is neglected and there is no success in solving the problems. The social services for the public, which are being implemented in Turkey, should be revised and brought to a point that will activate the internal dynamics of the society. It is possible to bring our own spiritual values to light and make them work. To follow the path drawn by these determinations, to ensure social welfare and to raise the principles of social peace, makes it necessary to enrich social work practices with spiritual elements.

In order to provide effective social work in the world and in Turkey, it is necessary to develop new social work intervention models with a multidisciplinary approach, suitable for social change, and to make necessary arrangements in accordance with the social state understanding. It is necessary to take action as soon as possible to strengthen the spirituality, protect and prevent the social deterioration in the family with all its aspects. The rapid change in the social structure causes moral destruction, and as a result of this, it creates the need for moral support units in every field such as health, education and security.

In the context of these evaluations, the following recommendations are made for practices in Turkey:

• In the social work discipline, Spiritual Support Departments should be established to prevent the deterioration of urban culture, and new service models should be developed for the spiritual needs and problems of the society, group, family and individual.

• In the face of social problems undergoing structural change, new social service units should be established in educational institutions for families with disabled and dependent children in educational environments as well as in health, taking into account local characteristics.

• The development of qualitative assessment scales that measure spiritual orientation in accordance with the social and cultural environment is considered necessary in order to make healthy and reliable interventions to the preferences of the client.

• It is necessary to develop structured interventions suitable for spiritual diversity in Turkey and to share the results of their implementation.

The isolation situation that arises when people living in modern societies, especially deprived of moral values, start to question why and for what purpose they live in such a society, can only be eliminated by revealing the spiritual social work practices of the public policies of the society.

In order to reduce the destructive effect of social problems in Social Service Institutions, it is important to apply Spiritual Social Work, which approaches people from a holistic perspective and increases sensitivity to all their material and moral needs, in all areas such as health and education.

Etik Beyan

"Care and Spiritual Social Work On The Axis Of Spirituality" başlıklı çalışmanın yazım sürecinde bilimsel kurallara, etik ve alıntı kurallarına uyulmuş; toplanan veriler üzerinde herhangi bir tahrifat yapılmamış ve bu çalışma herhangi başka bir akademik yayın ortamına değerlendirme için gönderilmemiştir.

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CHAPTER 2

HOMEOPATHIC TREATMENT

Eda Nur OKMAN[1] Süleyman KOZAT[2]

1 Arş. Gör. Van Yuzuncu Yıl University Faculty of Veterinary Medicine, Department of Internal Medicine
edanurokman@yyu.edu.tr ORCİD: 0000- 0001- 9016- 9739
2 Prof. Dr. Van Yuzuncu Yıl University Faculty of Veterinary Medicine, Department of Internal Medicine
skozat@yyu.edu.tr ORCİD: 0000-0001-5089-2623

1. Introduction

Alternative or complementary medicine is a treatment method with different concepts from current medical treatment methods and has become popular in recent years. Alternative medicine has different ideas from routine treatment and contemporary medicine. The demand for alternative therapies increased in the last several years and has gained popularity. (Chiu and Ho, 2005; Arlt et al., 2009; Kardanpour et al., 2016). Treatments developed on principles of medical medicine are often constrained in efficacy and too pricey. Accordingly, alternative medicine is approachable, does not necessitate high-cost laboratory conditions, and also natural and safer than medical medicine. Alternative medicine includes a variety of herbs, supplements, chiropractic, and homeopathic therapies (Stickel and Schuppan, 2007; Verma and Thuluvath, 2007; Henson et al., 2017). One of the treatment methods included in these alternative applications is homeopathy (Hadipour et al., 2017).

Homeopathy has a history of about 200 years and is named by combining the Greek words homeo, which means similar, and pathos, meaning suffering or disease. Homeopathy aims to provide the patient with a fast and permanent treatment protocol with natural methods that stimulate the body to heal itself (Özyurtlu and Aslan, 2007; Yaramış et al., 2016; Bhardwaj and Misra, 2018). One of the essential principles of this method is that similar substances can treat with similar matters [8]. The meaning of this fundamental principle, which constitutes the essence of homeopathy, is as follows: “When a substance is given to healthy people, it causes symptoms similar to the disease in those people, people who have that disease treated with this active substance (Ozçakır and Doğan, 2013).

2. History

Homeopathic treatment has dated back to ancient times. Since ancient times, information on the use of homeopathic principles has been found in ancient Egypt, China, the Incas, Aztecs, Native Americans, and Greek inscriptions (Vockeroth, 1999; Yarsan and Alim, 2015).

In 400 BC, Hippocrates was considered the father of medicine and treated similar things. In line with this principle, Paracelsus continued practices, one of the essential alchemists of the 16th century (Özçakır and Doğan, 2013; Yarsan and Alim, 2015). The German doctor Samuel Hahnemann developed homeopathy and named these principles in the literature in 1796 (Özçakır and Doğan, 2013). Carl Caspari published the first homeopathic guide documents in 1826. [14]. Hahnemann lectured on homeopathy at the University of Leipzig from 1811 to 1821. Fourteen years later, he moved to Paris and studied medicine (Rijnberk and Ramey, 2007). After Hahnemann, studies on homeopathy continued intensively,

and an American researcher named James Tyler Kent accept as the founder of modern homeopathy in the 19th century (Yarsan and Alim, 2015). Today and in the last century, homeopathic treatment is among the most frequently used methods in Western Europe, especially France, Germany, the Netherlands, and England (Pilkington et al., 2005).

3. Principles of Homeopathic Treatment

Homeopathy is a method of treatment based on the principle of "similia similibus curentur," which aims to activate the body's self-healing mechanism and treat it with similar things. According to homeopathic principles, every living organism can control diseases Velkers et al., 2005; Kacar et al., 2007; Camerlink et al., 2010). Hahnemann found this principle by using various doses of substances both in himself and in volunteers by applying trials and recording the effects of these substances in detail. Hahnemann used substances such as table salt (natrum muriatum), snake venom (Lachesis), head lice (*pediculus capitis*), and ivy venom in his homeopathic trials (Özyurtlu and Aslan, 2007; Rijnberk and Ramey, 2007). Hahnemann translated William Cullen's Lectures on Pharmaceutical Science into German but did not convince the author's explanation of the beneficial effects of quinine use in patients with malaria. Cullen said that quinine strengthens the stomach. Hahnemann also tried the quinine substance on himself and said that this substance produced similar symptoms with the symptoms of malaria. As a result of this observation, Hahnemann put forward the "Similia similibus curentur" theory (Rijnberk and Ramey, 2007). Hahnemann systematized this theory, established its principles, and shaped homeopathy (Pekmezci and Gültiken, 2015).

Homeopathy has based on three main principles. These principles are the similarity principle, the single remedy principle, and the minimum dose principle (Chiu and Ho, 2005). Homeopathic treatment aims to activate the reactions that will restore the organism's health by creating a warning with the effect of homeopathic substances and initiating the healing process (Kacar et al., 2007).

3.1. Similarity Principle

Hahnemann put forward the theory of "Similia similibus curentur."The symptoms that occur as a result of any disease are not the disease itself but the reactions of the organism to maintain homeostasis. For this reason, applying a symptomatic treatment as in traditional medicine does not eliminate the cause of the disease but only the symptoms it creates. According to homeopathic philosophy, the symptoms that occur in the case of illness are reactions that occur to adapt to infection and stress. For this reason, a substance that will cause the same symptoms when given to healthy people in high doses will activate the defense mechanism if

given in shallow doses (Vockeroth, 1999; Jonas et al., 2003; Clausen and Albert, 2010). This principle states that patients with a particular pattern of symptoms may cure if they administer a specific drug that produces a similar way of symptoms when given to healthy individuals [22]. Based on this view, instead of a treatment that will eliminate the symptoms, a treatment that strengthens the patient's life force by creating similar symptoms can be applied (Bonamin and Endler, 2010). To create a drug scale based on the principle of similarity, the results of drug trials in healthy people recorded, and a shallow dose of the drug that would cause the same symptoms given to sick people with similar complaints (Vockeroth, 1999; Pekmezci and Gültiken, 2015).

In high doses, coffee stimulates the nervous system and acts by increasing urine excretion. When it is prepared and given to the individual in homeopathic doses, it can be therapeutic for the sick person with nervous activity and insomnia problems. According to the similarity rule, the preparation called Aconitum causes an increase in body temperature when given to a healthy person in repeated doses. This drug can reduce fever when prepared in homeopathic doses and applied to individuals with a high fever. Although many people think of homeopathy as an herbal treatment, homeopathy uses all substances in nature to create its medicines (Özyurtlu and Aslan, 2007; Pekmezci and Gültiken, 2015).

3.2. The Single Remedy

Studies investigating the efficacy of homeopathic medicines carried out on a single drug. In the classical homeopathy developed by Hahnemann, only one drug matches the appearance and symptoms of the disease used; different drugs cannot be mixed. In the case of multiple drug use, it is not known which medication will be responsible for the effects. As a result of administering more than one drug, the total product will not increase; on the contrary, they will prevent each other's products (Pekmezci and Gültiken, 2015).

3.3. Minimum Dose

One of the factors affecting the success of homeopathic treatment is the minimum dose principle. According to this rule, homeopathic medicines given in minimum doses can activate the body's healing power and are similar to the symptoms seen in the patient (Kumari et al., 2016). The effect of homeopathic medicines manifests in minimum but most effective doses to support the body's natural healing process and restore the body's balance. Homeopathic medicines in minimum quantities stimulate the body to heal without any toxic effects. Since high doses may affect the healing power above the perception potential, treatment failure may occur, especially for patients with reduced vitality (Katz, 1995; Zimmerman, 2012; Pekmezci and Gültiken, 2015).

4. Homeopathic Drugs

Homeopathic medicines obtain by diluting herbal, mineral, and animal origin ingredients. These are red onion, arnica (mountain grass), white arsenic, poison ivy, belladonna, and stinging nettle (Yarsan and Alim, 2015; Kumari et al., 2016). Prescribing and preparation of homeopathic medicines based on the individual's overall symptoms. There are homeopathic preparations for liquid (ampoule, drops) or solid (ointment, tablet, globule-spheres). They can administer subcutaneously, intramuscularly, locally, or orally (Mathie and Clausen, 2014). Mineral-based medicine ingredients are gold, arsenic, phosphorus, zinc, and calcium substances. Atropa belladonna, Arnica montana, Calendula officinalis use as herbal substances in homeopathy. Animal origin ingredients are snake, bee, dog milk, blood, cartilage tissue, umbilical cord and embryo, pus, the saliva of a rabid dog, scabies agents, tuberculosis discharges, or diseased tissues as cancer tissue (Özyurtlu and Aslan, 2007; Yarsan and Alim, 2015; Pekmezci and Gültiken, 2015).

5. Preparation and Administering of Homeopathic Drugs

Raw materials of vegetable, animal, and mineral origin are used to obtain homeopathic medicines. These raw materials must be first made into the primary material. For this purpose, a suitable vehicle such as alcohol or water is poured onto the raw materials and waited. A primary pharmaceutical substance such as powder, extract, a tincture is obtained by separating the dissolved parts. The primary substance obtained is diluted to make it suitable for use and is turned into forms such as ointments, drops, tablets, injectable solutions. Subjecting the primary substance to the dilution process ensures that its toxicity and side effects are reduced, and the harmful substances in the content are neutralized (Özyurtlu and Aslan, 2007; Yarsan and Alim, 2015; Pekmezci and Gültiken, 2015). The dilution of the primary substance is done by serial dilutions and shaking. This dilution process is called potentiation. There are two commonly used dilution scales, X or decimal and C or centesimal. X potencies (Ullman and Ullman, 2005). X potencies are diluted 1 to 9, and C potencies are diluted 1 to 99. To make an X potency, 1 part of the original substance is added to 9 parts of solvent, and to make a C potency, 1 part of the original substance is added to 99 parts of the solution (Castro, 1996; Ullman and Ullman, 2005). The X in the name of the preparation (e.g., Arnica 6X) means that the dilution is 1/10, and C indicates that the dilution is 1/100. The number next to X and C indicates how many times the substance has been diluted. In addition to the X and C potencies, XM and LM potencies are obtained with 1:10 000 to 1:50 dilutions (Kacar et al., 2007; Yarsan and Alim, 2015).

Homeopathic remedies are often formulated in small tablets or chewing gums. Since the drugs in solid and liquid pharmaceutical form have no taste, administering these drugs to the patient is relatively easy. In homeopathy, when adjusting the dose of the medicine, the individual should be evaluated holistically; not only the diseased organ but also the individual's personality, character, and behavior should be considered as a whole. Adjusting doses is not related to the individual's weight (Vockeroth, 1999; Hektoen, 2005). In homeopathy practices, each patient is unique. In selecting the drug, the drug in the lowest dose that can be effective on the patient should be chosen, suitable for the patient's history and symptoms (Özcakır and Doğan, 2013).

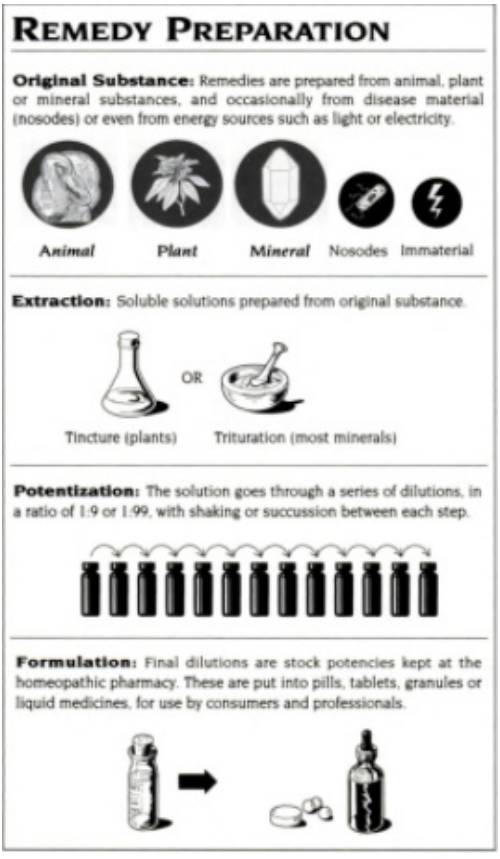

Image 1. *Remedy Preparation (Hershoff, 1999)*

4. Mechanism of Homeopathic Drugs

Data on how homeopathic medicines reveal their therapeutic effects is still unclear, but some theories about how they work (Loken, 2002). Homeopathic medicines are obtained by a mechanism called potentiation. The main ingredients are continuously diluted and shaken countless times

so that only a tiny fraction of the original substance is present in the final product. Homeopaths have observed that the more the active ingredient is diluted and shaken, the more effective it will be, and fewer drug doses will be required for treatment. Although the amount of homeopathic medicine given to the patient is low, it activates many bioenergy systems in the body because it has high internal energy (Vockeroth, 1999; Mazocchi and Batisti, 2002; Pekmezci and Gültiken, 2015;). According to the researchers, the effectiveness of homeopathic substances is not related to the number of molecules they contain. It is argued that this activity is related to the energy generated during the preparation of homeopathic remedies and that another energy can affect the energy (Özyurtlu and Aslan, 2007). Another working mechanism of homeopathic medicines is similar to applying attenuated microorganisms (vaccines) to the human body to trigger the immune response (Kardanpour et al., 2016). For the homeopathic treatment to be effective, the patient's symptoms should be compatible with the homeopathic medicines. It should be checked whether the patient has any signs of another disease (Castro, 1996; Özyurtlu and Aslan, 2007).

Symptoms	**Homeopathic Drug name**
Colic	Colocynth 30C, Bryonia 30C, Kalibich 30C, Pulsatilla 30C, Graphites 30C, Ipeca 30C, Nux vomica 30C
Diarrhea	Ipeca 30C, Emetine 30C, Mercurius sol. 30C, Phosphorus 30C
Anemia	China 6X or 30C, Arsenicum album 30C, Phosphorus 200C, Calcarea carbo 1M, Psorinum 200C
Anorexia	Nux vomica 30C, Lycopodium 30C, Pulsatilla 30C, Ferrum phose 6X, Sulphur 30C
Gastritis	Pulsatilla 30C, Nux vomica 30C, Lycopodium 30C
Allergic conditions	Euphrasia 30C, Urtica urens 30, 200, Rhus Toxicodendron 30, Sepia 30, Arsenicum album 30C, Ipeca 30 or 200C, Lachesis 200C
Asthma	Cassia sophera Q, Aconite Q, and Ipeca Q, Tuberculinum 1M, Thuja occidentalis 200 or 1M, Arsenicum album 30C, Thyroidin 1M, Sulphur 200 or 1M, Nux moch 30 or 200, Urtica urens 30

Table 1. *Some Homeopathic Drugs (Yarsan and Alim, 2015).*

5. Homeopathy Use in Medicine

Complementary and alternative treatment methods have been widely used in treating human diseases in recent years. Alternative therapies in medical medicine are primarily used to treat chronic conditions (Hektoen, 2005). Homeopathy is a suitable method for treatment in many cases where classical medicine is insufficient. One of the uses of homeopathy in human medicine is dentistry. Homeopathic medicines relieve pain, inflammation,

and bleeding after tooth extraction. For this purpose, drugs named Arnica montana, Hydratis, Canadensis, Belladona 30C, and Calcarea carbonica 30C are applied in various ways in the treatment of gingival bleeding, aphthous ulcers, dental abscesses, and dental caries. Homeopathy is not a substitute for dental medical methods, it helps to relax the patient and facilitate the procedure (Kardanpour et al., 2016). Natrum muriaticum, a homeopathic medicine, was used in African malaria individuals, and it was determined that malaria attacks decreased in individuals treated with this medicine (Davies, 2007). Homeopathy is more effective than classical methods in treating upper respiratory tract diseases in human medicine and gives positive results. Homeopathy is preferred more often than classical methods to relieve self-limiting chronic diseases (Erlewyn- Lajeunesse, 2015). Another use of homeopathy in human medicine is psychotherapeutic treatment. Positive data have been obtained in studies on homeopathic medicines in this area (Johannes et al., 2013). Homeopathic medicines Ruta graveolens 5CH and Rhus Toxicodendron, which are used in the early stages of breast cancer, showed positive effects in reducing joint pain and involvement after three months of treatment (Karp et al., 2016). Homeopathic preparations were obtained by preparing 30 to 50 diluted solutions of HIV in individuals with HIV, and researchers investigated the effect of these drugs on the immunological parameters of the patients. Researchers detected significant relief in the patients' symptoms, weight gain, and an increase in their living standards were detected (Shah, 2016).

6. The Considerations When Administering Drugs

Some conditions should be considered during the application of homeopathic medicines. The patient should inform the homeopathy practitioner about the drugs he has taken or will take before the homeopathy treatment. If the patient takes any other homeopathic medicine, they should tell the homeopathy practitioner. During homeopathic treatment, the patient should stay away from some substances. Substances such as coffee aromatic and essential oils can negatively affect homeopathic treatment. Oral or topical antibiotics, steroids, and narcotics should be avoided during homeopathic treatment (Ullman and Ullman, 2005).

7. Homeopathy Around the World

Homeopathy has existed since ancient times. As a result of research, it has been determined that the sources for its first use in the world are ancient Egypt, China, Incas, Aztecs, and Native Americans (Vockeroth, 1999). When Doctor Hahnemann, the founder of homeopathy, died in 1843, homeopathic treatment began to be recognized worldwide (Castro, 1996). Homeopathy's popularity has increased globally since the 19th century and has started to be applied in various countries. It entered the

United States in the 19th century and was implemented in the 20th century (Castro, 1996; Rijnberk and Ramey, 2007). homeopathy is practiced in many continents and countries today. [29]. Except for some countries in Europe, homeopathy maintains its popularity to a large extent and finds many application areas. Homeopathy retains its popularity with thousands of practitioners in Germany and is widely used for prophylactic purposes. It is reported that 27% of 57,000 types of drugs used in the human field in Germany belong to homeopathic medicine. France is more in demand for homeopathy than other European countries and prescribes various homeopathic medications to its patients. Homeopathy is used very often in Northern Europe. It is reported that 37% of Norwegians apply homeopaths, and there has been an increase in applications in the last 20 years. In Switzerland, there has been an increase of 5% to 24% in the use of homeopathy (Castro, 1996; Özyurtlu and Aslan, 2007; Özcakır and Doğan, 2013). Homeopathy began to spread rapidly in Australia and New Zealand. Homeopathy hospitals were opened in England. South America has started to respect homeopathy, especially Mexico, Brazil, and Argentina, and they have begun to practice homeopathy. Homeopathy finds its application area with 120 schools and 100,000 practitioners in India (Ullman and Ullman, 1995; Castro, 1996; Özcakır and Doğan, 2013). In Turkey, homeopathic substances are not as every day as in European countries, but homeopathic substances have become widespread compared to previous years (Özyurtlu and Aslan, 2007).

8. Advantages and Disadvantages of Homeopathic Treatment

Homeopathy is an alternative treatment option to conventional treatment methods in animals and humans. Reducing the methods applied by combining classical antibiotic and steroid treatment makes homeopathic and alternative methods advantageous (Searcy et al., 1995). Homeopathy is a therapeutic method that leaves no chemical residues in the environment, has no toxic or toxic properties, and enables all organisms to maintain good health. Homeopathic remedies are completely safe and non-poisonous (Özyurtlu and Aslan, 2007; Santa Rita et al., 2016). With the effect of homeopathic substances, the organism is stimulated, and thus the healing process is initiated. Homeopathic medicines can be used safely in pregnant women and children without causing any side effects. In addition, they do not show any undesirable effects when used with other treatment methods (Kacar et al., 2007; Özyurtlu and Aslan, 2007). Homeopathic remedies are derived from natural ingredients. They work in harmony with the immune system and the nature of the body. Homeopathic medicines are not addictive, and while treating all symptoms, they produce solutions by acting on the leading cause, not according to the symptoms (Yarsan and Alim, 2015). Homeopathic treatment contributes to the organism's health

by using the body's healing power. Homeopathic medicines are prepared according to the minimum dose rule. For this reason, it is reported that they do not cause addiction in the organism (Kumari et al., 2016).

Homeopathic treatment has advantages as well as disadvantages. Homeopathy is the most expensive treatment method among alternative treatment methods. They should not be used uncontrolled and for a long time; otherwise, side effects may occur. The primary treatment is not applied when the symptoms are treated instead of the disease (Kuru and Oral, 2013; Orjales et al., 2016).

As a result, Homeopathy, an alternative medicine method discovered in the 19th century, has been widely used to treat many diseases until this time and has been a method of both alternative and medical medicine for many patients. Homeopathy practices are always more advantageous and more successful when compared to traditional medical techniques. For this reason, homeopathy will continue to be among the treatment methods with minor side effects among alternative medicine methods.

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CHAPTER 3

SYSTEMATIC REVIEW IN EVIDENCE-BASED MEDICINE

Yusuf DİLBİLİR[1], Sadi ELASAN[2]

1 Hakkari University, Vocational School of Health Services, Hakkari, Turkey yusufdilbilir@hakkari.edu.tr ORCID:0000-0002-4569-251X
2 Yuzuncu Yil University, Faculty of Medicine, Department of Biostatistics, Van, Turkey sadielasan@yyu.edu.tr ORCID: 0000-0002-3149-6462

EVIDENCE-BASED MEDICINE

Rapid developments in the field of medicine require physicians to constantly update their knowledge. Every day, new treatment methods, types of medical interventions, laboratory tests are emerging and new methods are being replaced by old methods. Physicians follow the relevant literature and research to keep their knowledge up to date (Zoccali, 1999). In this context, evidence-based medicine practices; the need for new information is rapidly spreading and gaining importance due to reasons such as reaching the truth most reliably, encouraging scientific and critical thinking.

Evidence-based medicine practice is an approach that dates back to the middle of the 19th century and continues to be up-to-date. Evidence-based medicine is the practice of integrating the best scientific evidence with the clinical experience of the physician and the patient's values (Sackett et al., 1996). Evidence-based medicine; is objective information compiled from scientific sources with the best evidence available through systematic research. In other words, it is the honest and logical combination of professional experience and cases within the framework of medical ethics.

According to Sackett et al., (1996), one of the pioneers of evidence-based medicine; A good physician can combine his clinical experience with the most reliable scientific evidence when making a decision. To achieve this integration, physicians must have the skills to access scientific evidence, critically evaluate evidence, and put reliable data into practice (Williamson et al., 1989). As in many fields of science, the results obtained in the field of medicine must be evidence-based. Contemporary medicine practices are also based on the results of observations and experiments made with scientific methods, that is, on evidence (Uysal, 2019). Evidence-based medicine is a practice that integrates the best scientific evidence, using specific methods, with the clinical experience of the physician and the patient's values, and makes it clinically applicable.

The most basic rule in evidence-based medicine practices is to obtain the most appropriate and valid evidence to solve the clinical problem. Access to scientific publications describing the evidence for solving problems in the field of medicine has also become much easier thanks to the internet. In addition, daily problems that physicians are responsible for solving (eg patient burden) are also increasing. For this reason, it is not possible for every physician to follow all publications containing evidence in their field. In this case, it would be more practical to use methods such as meta-analysis, systematic review, diagnosis and treatment guides, which are secondary information sources developed to obtain more practical and quality evidence, instead of obtaining evidence directly from primary sources of information (scientific articles, etc.). Experts working on this

subject not only determine the scientific values of the publications in the primary information sources but also examine the publications on the same subject comparatively and create secondary information sources that include integrated evidence such as systematic review, meta-analysis, diagnosis and treatment guidelines (Uysal, 2019). Thus, physicians can quickly access up-to-date and valid evidence for certain medical problems.

Basic Steps of Evidence-Based Medicine Practice

Evidence-based medicine practices; consists of effective methods for accessing, evaluating and applying information. Five important steps to be followed in evidence-based medicine practices are given in Figure 1.

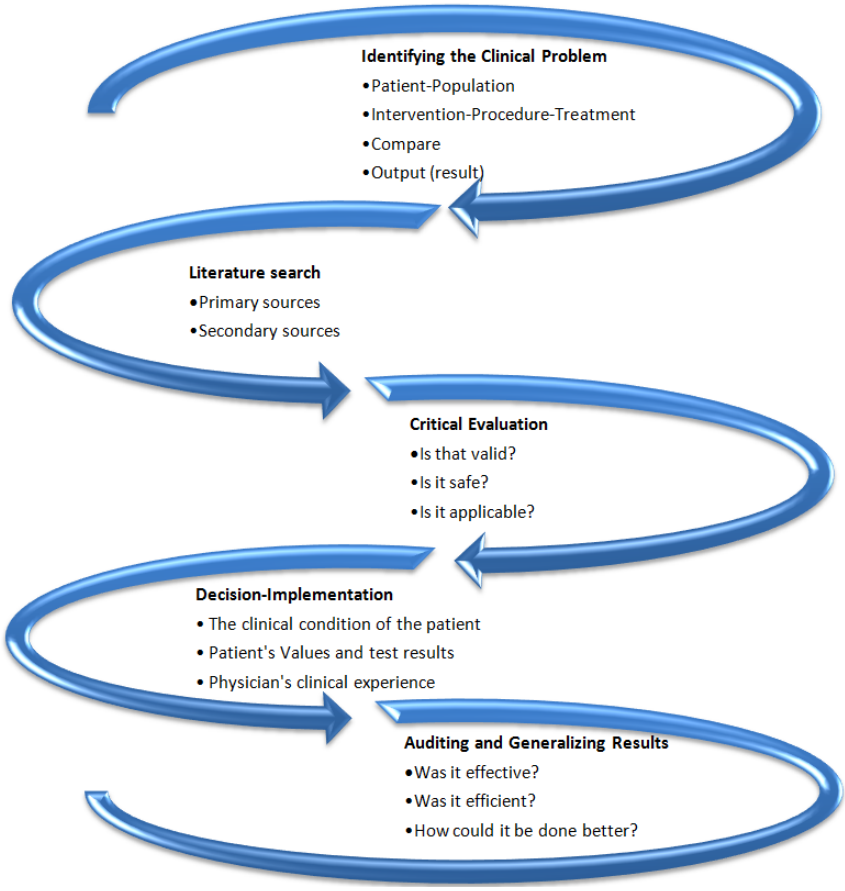

Figure 1. *Basic Steps of Evidence-Based Medicine Practice*

1. **Identification of the Clinical Problem**

As the starting principle of evidence-based medicine practices, the information needed to solve the problem or uncertainty encountered while evaluating the patient in the clinic is transformed into answerable clinical

questions. After the questions are determined, the search for appropriate evidence for the solution can be started (Demirkan et al., 2000). These questions vary according to the purpose of the study and are also effective in determining the type of research. Therefore, the questions are; These are questions created to obtain or evaluate information about clinical findings, etiology, prognosis, treatment, prevention, differential diagnosis, diagnostic tests and personal development.

In the study conducted by Richardson et al., (1995), the research question was defined with four features abbreviated as PICO (Aşık & Özen, 2019). The PICO formula, which is explained below, is used in the formation of clinical questions.

P: Patient/population

I : Intervention (intervention-operation-intervention)

C: Comparison (Comparison/alternative intervention or treatment)

O: Outcome (result).

2. Literature Review

In order to answer the questions determined in the first step, primary and secondary sources are searched and the most useful, reliable and quality evidence is searched (Sackett et al., 1996). In obtaining this evidence; It is recommended to follow evidence-based medical journals and books, use computer decision support systems and search bibliographic databases.

The main barriers that physicians voiced in seeking evidence are; time constraints, the lack of necessary training for the effective use of databases, and the fact that some databases can only be accessed with a paid membership (Green and Ruff, 2005). In terms of access to information, knowing which databases contain reliable evidence-based information and how to reach the most relevant studies to solve the problem in the databases as soon as possible are important factors. Therefore, in the search for evidence; The steps should be followed to determine keywords with the PICO formula, to create search strategies by combining keywords with Boolean operators (AND, OR and NOT connectors), and to search by selecting reliable databases (Çakmakkaya, 2018). The level of knowledge of researchers about how to perform these stages will greatly affect the process and outcome of their research.

While searching for an answer to a problem, the sources and research types with the highest power of evidence should be emphasized (Şenocak, 2009). Physicians should be knowledgeable about the level of evidence of research types. In terms of the strength of scientific evidence, the types of research are listed in Figure 2 from strong to weak.

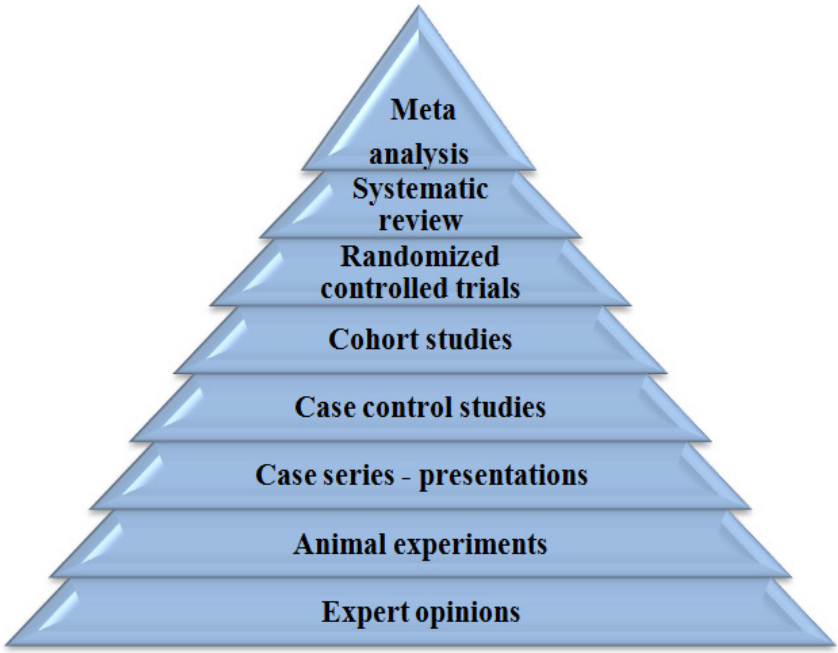

Figure 2. *Evidential Power Pyramid*

3. **Critical Evaluation**

Concepts such as validity, reliability, efficacy, clinical significance and applicability of the obtained evidence are investigated. These concepts need to be evaluated from a critical perspective. If the evidence does not meet these criteria sufficiently, the previous steps are returned and new evidence is tried to be obtained. After the critical evaluation phase of the evidence is completed, a practical application can be started.

4. **Decision and Implementation**

It is important how useful the evidence expected to be an answer to the medical question will be to the patient and how much it will affect the health service to be given to the patient within the framework of the patient's expectations and preferences. However, the physician's ability to use clinical competence to quickly determine a patient's health status, individual risks, benefits, and expectations from potential interventions is also a cornerstone of the decision and implementation phase (Sackett et al., 1996). Clinical experience is not sufficient unless supported by the best scientific evidence. Similarly, without knowledge and experience, it cannot be predicted how clinical evidence will be applied to the patient. Therefore, the evaluation of the best evidence obtained; is the stage where the patient's clinical status, diagnostic test results, patient-specific values, and the physician's experience are compared. The most appropriate answer

to the medical problem is found and applied by combining the information about the medical problem encountered with the most appropriate evidence.

5. **Auditing and Generalizing Results**

Evidence from the practice of evidence-based medicine may invalidate some previously accepted diagnostic tests and treatments. After the practice of evidence-based medicine, new methods and practices that are stronger, more accurate, more precise and more reliable can be substituted for the old methods. A good physician uses a combination of individual clinical experience and the best external evidence. Because these alone are not enough. Personal experience and consulted external evidence should be consistent with clinical judgment (Sackett et al., 1996). In this sense, it should be emphasized that the evidence obtained from clinical studies supports physician experience and is not an alternative to experience. The last step of evidence-based medicine is the stage of checking the compliance of the evidence to the patient (Demirkan et al., 2000; Şenocak, 2009). The availability of evidence depends on whether it matches the physician's clinical experience and the patient's condition. In addition, the evidence obtained for the medical question needs to be evaluated in terms of efficacy, efficiency and medical ethics.

SYSTEMATIC REVIEW IN EVIDENCE-BASED MEDICINE PRACTICES

Systematic review; It is a structured and comprehensive synthesis of a large number of studies done by similar methods to determine the best research evidence available by experts in the field. The importance of systematic review in terms of health is increasing as it is a research method that produces the strongest evidence in evidence-based practices. Healthcare professionals and physicians can make more reliable clinical decisions using the strongest research evidence available. In order to produce and use stronger evidence, systematic review studies can be planned and conducted with a correct methodology.

Stages of preparing a systematic review; It consists of defining the work, scanning for information, evaluating and analyzing the quality of evidence, presenting and summarizing the evidence, discussing the evidence, writing the systematic review, external referees and publishing (Karaçam, 2013). Health professionals, the strong evidence they obtained through systematic review studies; They can use existing practices to change and increase the effectiveness of clinical care, to provide better quality and reliable care, to create care guides and to reduce costs.

Systematic Review; to find an answer to a research question prepared on a certain subject, it is systematically and unbiasedly scanning the studies

on the same subject by the determined criteria, evaluating the validity of the studies found and combining them by synthesizing. The systematic compilation, when properly done and reported, adds enormous value to the healthcare knowledge base. Systematic reviews and meta-analyses are at the top of the evidence pyramid and can have implications for clinical practice guidelines. Considering the abundance of resources in the field of health and the limited time of researchers, it is understood how important a role the reviews have in decision making. At the same time, with systematic reviews, topics that need to be researched in the future, gaps in the literature or areas that have been insufficiently studied can be identified. A good review is a unique resource that will contain all the available evidence for the research question of interest. Systematic reviews are considered the gold standard because they contain a more detailed literature review and have less author bias (Yannascoli et al., 2013; Oermann, 2015; Çınar, 2021). Therefore, the place of systematic reviews in evidence-based medicine is becoming increasingly popular.

The purpose of systematic compilation is not just to collect all the information. A systematic review is created by comprehensively scanning the relevant studies and using various acceptance and rejection criteria to determine which studies will be included in the review in an unbiased manner, and by synthesizing the information contained in these studies. Although systematic review studies are superior in terms of evidence, if they are not performed in accordance with the systematic review methodology, the risk of bias increases and creates limited information for decision-makers. In particular, the inadequacies in the methodological quality of the included studies and the problems in reporting lead to inadequacy or contradictions in the interpretation and generalization of the research results and do not constitute strong evidence for clinical decisions.

Basic Stages of Systematic Review

The main stages of systematic compilation; creation of the research question, determination of inclusion and exclusion criteria, protocol process, use of clear and repeatable methods, comprehensive literature review, evaluation of the quality and validity of the data, systematic synthesis of the findings, interpretation and reporting (Nahcivan and İncirkuş, 2018; Moller and Myles, 2016; Davies, 2011; Cinar, 2021).

1. Formation of the Research Question

The first step of making a systematic compilation; is to define the problem that needs to be addressed in the form of a clear and structured question. Since the search strategy is built on the compilation question, formulating the compilation question is crucial to developing the search strategy. Before asking “how” to prepare a review, it is important to

ask "why". Evidence-based practice questions focus on real problems. Successful retrieval of relevant information begins with a clearly defined, well-structured question (Uman, 2011; Davies, 2011; Khan et al., 2003; Cinar, 2021). A standard format or framework for asking questions helps to focus on the essentials.

The concept of PICO was defined by Richardson et al., (1995) to categorize clinical questions into searchable keywords. Schardt et al., (2007) also referred to the question type and the best study design to answer the identified question and presented the PICOS model. Using the PICOS model as a search strategy tool improves the quality of literature reviews. The framework of the research question is determined. Research question; P: Population, I: Interventions, C: Comparators, O: Outcomes, and S: Study designs should be clearly defined. These components of the research question are briefly called PICOS (Yannascoli et al., 2013; Uman, 2011; Davies, 2011; Khan et al., 2003; Nahcivan and İncirkuş, 2018; Çınar, 2021).

1. Inclusion and Exclusion Criteria

Once the study question is finalized, authors should establish a comprehensive list of inclusion and exclusion criteria. Considering the components of the research question, "inclusion and exclusion criteria" are defined. To avoid selection bias, inclusion and exclusion criteria should be determined before data collection and analysis. Strict criteria are required to identify eligible articles to include. When making a Systematic Review, it is important that authors clearly define the studies they will select and exclude. For topics well represented in the literature, only articles with a high level of evidence should be included. However, low-level studies may be included if not much work has been done in the area relevant to the review question. (Yannascoli et al, 2013; Uman, 2011; Karaçam, 2013; Khan et al, 2003; Oermann and Hays, 2015; Çınar, 2021). In addition, the limitation of the year of publication will also be important. A decision needs to be made whether to include human and/or animal studies.

1. Determining the Protocol Process

Systematic compilation studies are important research projects and must be done within a specific protocol. It is stated both in the reports of international evidence centres and in publications that the systematic compilation process should be planned and carried out within the framework of a certain plan and protocol (Nahcivan and İncirkuş, 2018). The protocol ensures that the compilation follows a clear plan and specifies the methods to be used in order to minimize bias (Oermann and Hays, 2015). PROSPERO (International Prospective Register of Systematic Review) is a systematic review registry system funded by the UK National Institute of

Health Research. PROSPERO; It aims to avoid duplication, reduce the risk of bias by allowing comparison with studies whose planning phase has been completed in the protocol, and provide a comprehensive list of registered systematic reviews. At the same time, providing free and open access to information on ongoing systematic reviews, promotes transparency in the systematic review process and helps prevent undesirable duplication of the subject (Uman, 2011; National Institute for Health Research, 2022). PROSPERO gives a registration number for each registered systematic review. This number can be displayed in publications and reports. This trick also makes it possible to track the subsequent use of the assembly and monitor its effects.

2. Comprehensive Literature Review

It is defined as the systematic review and critique of publications containing information on a particular subject. A well-structured literature search is the most effective and efficient way to find solid evidence on the subject under investigation. The most important task in the search process is to determine the keywords well and to use them correctly. Research questions should be based on the creation of keywords. MeSH (Medical Subjects Headings) for English keywords and TBT (Turkey Science Terms) for English keywords can be used (Uman, 2011; Karaçam, 2013; Oermann and Hays, 2015). In order to narrow the search, if my keywords are used side by side beyond being used together, the phrase should be written between two quotation marks (“ ”). Space can be delimited using Boolean connectors (Boolean connectors: and, or, not). “And” retrieves results containing all search terms; “or” means that the results must contain at least one of the search terms. “Not” excludes citations for the chosen term (Oermann and Hays, 2015). Literature review constitutes the most important part of academic research. At this stage, every step taken consciously and correctly brings scientific benefits to the researcher (Karaçam, 2013; Çınar, 2021). Studies obtained using bibliographic software are recorded and stored.

3. Selecting Databases

After selecting and narrowing down the topic, the next step is to select the most appropriate databases for searching. Identifying databases for searching (MEDLINE, Web of Science, Pubmed, Science Direct, CINAHL, Scopus, Cochrane, TUBITAK, Medline, TR database etc.) is an important decision for authors not to miss critical articles.

4. Data Extraction and Quality Investigation

According to the PRISMA flowchart, the selection process consists of three steps. These steps include the evaluation of the title, abstract

and full texts of the study. The most basic recommendation in order to increase the reporting quality of the review along with the methodological quality in the compilation process is to use standardized tools that show that the compilation method is complied with both during the compilation process and at the publication stage. Evaluation of the quality of the study is an indication of the strength of the evidence provided by the systematic review and informs the necessary standards for future research. It is recommended to use the PRISMA Declaration (The Preferred Reporting Items for Systematic Reviews and Meta-Analysis), which is a 27-item checklist and 4-stage flow chart developed by international organizations and experienced authors and to comply with the articles in this declaration. The "Cochrane Guide to Systematic Reviews" is a fundamental resource for those who conduct systematic reviews and meta-analyses (Cochrane Handbook for Systematic Reviews of Interventions, 2011). The pattern of studies included in the systematic review should be considered in determining the quality assessment tool. Quality assessments for each study are carried out independently by at least two researchers. As a result of the evaluation; Studies with "strong" and "moderate" scores are included in the systematic review (Yannascoli et al, 2013; Uman, 2011; Karaçam, 2013; Khan et al, 2003; Nahcivan and İncirkuş, 2018; Çınar, 2021). Thus, qualified studies will be used as a source.

5. Reporting Results

PRISMA guidelines should be used when reporting a systematic review or meta-analysis. Using PRISMA improves the quality of the review report. Thus, an international standard can be achieved in reporting. Flow charts should be presented as figures along with the text. In the systematic review findings of the authors; should present a report of study selection, characteristics of studies, results of analysis of the risk of bias in studies, and synthesized findings of studies. Tables are the preferred method of presenting findings. In the discussion, the authors should express how working together with the strength of the evidence contributes to the evidence (Yannascoli et al, 2013; Karaçam, 2013; Oermann and Hays, 2015; Khan et al, 2003; Nahcivan and İncirkuş, 2018; Çınar, 2021). The discussion section should also include difficulties and limitations in obtaining studies.

6. **Summarizing the Evidence**

The findings synthesized in a clear and understandable way are listed and summarized. The findings should indicate the objectives of the systematic review, and the most important comparisons and conclusions should be highlighted in the text. The characteristics, findings and data analysis methods of the studies are given in tables and figures. Tables

and figures should relate directly to the findings section of the systematic review. In a flowchart, it is recommended to present the number of studies screened in the systematic review, those that were eligible and included in the review, the studies that were excluded, and the reasons for exclusion (Cochrane Handbook for Systematic Reviews of Interventions, 2011; Higgins and Green, 2011; Moher et al., 2009). In this context, the results will have the quality of scientific evidence.

7. Debate of Evidence

Checklist for discussion section; The main findings of the systematic review, the strengths and weaknesses of the systematic review, the strengths and weaknesses of the evidence, the discussion of the findings within the framework of the existing evidence, the applicability of the findings, the inclusion of the findings in practice and the clinic, the suggestions for further research, and the conclusion (Karaçam, 2013).

8. Presentation of the Systematic Review

In the international literature, it is recommended that the presentation of systematic review and meta-analysis research (writing the research report) be made according to the PRISMA Statement checklist. The purpose of the PRISMA Statement is to assist authors in improving the presentation of systematic reviews and meta-analysis research. In addition, the PRISMA Statement can be used for the critical evaluation of published systematic reviews and meta-analysis studies (Moher et al., 2009; Karaçam, 2013). Considering the checklist from the first stage of preparing the systematic review would be a much more accurate approach, especially in meeting the requirements of the research methodology.

CONCLUSION

Evidence-based medicine has enabled the evaluation of much literature, data, and evidence obtained through a scientific filter, as the ways of accessing information have increased today and it is not difficult to reach a study conducted anywhere in the world on the subject being studied. Evidence-based medicine is a new field in which traditional medicine is supported by the best evidence and clinical studies are evaluated together with reliable diagnostic tests, valuable prognostic markers and efficacy of treatment. Although the inadequacy of traditional information sources about the need for new information, the limited time to read medical journals, the difficulties encountered in reaching meaningful information that will meet the needs of physicians from large literature data and delivering this information to research and education may seem restrictive in settings, especially in the diagnosis and treatment stages, strategies aiming at lifelong learning are still in use. and the development

of systems that enable the delivery of information to physicians within seconds accelerates the evidence-based medicine process (Sackett et al., 1996). In evidence-based medicine practices, it will be more practical to use secondary information (such as meta-analysis, systematic review, diagnosis and treatment guidelines) developed to obtain more practical and quality evidence instead of obtaining evidence directly from primary sources of information (scientific articles and studies).

One of the most important processes in evidence-based medicine practices is a systematic review. Conducting and publishing a systematic review requires a research team including a researcher experienced in writing a systematic review, cooperation among team members, systematic work from the planning stage, necessary and sufficient time for the study and a determined effort (Yannascoli et al, 2013; Uman, 2011; Karaçam, 2013; Moller and Myles, 2016; Çınar, 2021). Systematic reviews that are not made in accordance with the standards cannot be expected to meet the expectations of the readers. By contrast, well-structured and standardized systematic reviews are at the forefront of evidence-based medicine and present the available evidence for the research question of interest. In this study, "Systematic Review in Evidence-Based Medicine" is outlined and the steps to be followed in the implementation phase and the importance of these steps are emphasized. In the study, the benefits of systematic review processes, which are very popular and widely used in evidence-based studies, are stated for the researcher. It would be beneficial to include more systematic review studies within the scope of "evidence-based medicine" in our country as well as all over the world.

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CHAPTER 4

ENDOSCOPIC THIRD VENTRICULOSTOMY

Abdulkadir DEMİR[1], Necati ÜÇLER[2], Evren SANDAL[3]

1 Adıyaman Training and Research Hospital, Neurosurgery Department, ORCID ID 0000-0001-9075-6124, ademirmd@yahoo.com
2 2Gaziantep University, Faculty of Medicine, Neurosurgery Department, ORCID ID 0000-0002-3882-5819, necati_ucler@yahoo.com
3 İzmir Medicana International Hospital, Neurosurgery Department, ORCIF ID 0000-0001-9268-1744, drevrensandal@hotmail.com

Introduction

Endoscopic third ventriculostomy (ETV) is one of the basic surgical techniques used in the treatment of hydrocephalus. It is aimed that the Cerebrospinal Fluid (CSF) will pass into the basal cisterns by bypassing the obstruction with the help of a hole (stoma) opened in the base of the 3rd ventricle (tuber cinereum) with the help of neuroendoscope.

History

The concept of ETV began to be discussed at the beginning of the 20th century and since then, with the increase in technology and surgical experience, it has taken an important place in the treatment of hydrocephalus.

The first endoscope used in history was presented by the German urologist Maximilian Carl-Friedrich Nitze in 1879 as the Nitze-Leiter cystoscope. This invention gave neurosurgeons the opportunity to enter the ventricle. The first neuroendoscopic intervention was used by Lespinasse, a urologist, in 1910 with the aid of a cystoscope. In this operation, the choroid plexuses of two patients with hydrocephalus were destroyed. By 1922 Walter Dandy imaged the ventricles and noted the lateral ventricle, foramen monro, choroid plexuses, and vascular structures within the ventricle. The term "ventriculostomy" was first used at that time. With the subfrontal approach, the anterior wall of the third ventricle, the lamina terminalis, was used, but the patient's optic nerve had to be sacrificed. He tried this method in 6 patients, but it was unsuccessful (1).

In 1923, William Jason Mixter performed the first successful ETV for the treatment of obstructive hydrocephalus using a ureteroscope. The patient's head circumference decreased and the pressure between the ventricles and the cisterns was equalized. In the same year, Temple Fay and Francis Grant succeeded in taking black and white images of the ventricles without any complications (2).

Years later, in 1934, Tracy Putnam introduced the 3-channel ventriculoscope (one with light source and 2 for cauterization) and, like Dandy, performed a choroidal plexotomy. In 1935, John Scarff took Putnam's ventriculoscope a step further and added an irrigation system, preventing the ventricles from collapsing by keeping the intraventricular pressure the same during the procedure (1,2).

In 1949, Frank Nulsen and Eugene Spitz discovered a different way of treating hydrocephalus, the shunt system. Excess CSF was sent to the atrium or peritoneal cavity with the help of catheters (3).

French neurosurgeon Gerard Guiot performed the first successful ETV in history on 8 August 1962 in a 40-year-old patient. In the following years,

flexible endoscope was found and Takanori Fukushima performed the first ventriculostomy with ventriculofiberoscope in 1973. By the beginning of the 2000s, it was started to be performed with stereotaxy and possible vascular damage was minimized (4).

As a result of the developing technology and experience, the ETV success score was defined and it became a guide in predicting the success of the process (5).

One of the most recent contributions to all these developments was added by Benjamin Warf. Warf concluded in his studies that ETV and choroid plexus cauterization (ETV-CPC) were more successful than just ETV (6).

Anatomy

The ventricular system, which provides the circulation of CSF in the brain tissue, consists of a series of channels. CSF produced in the choroid plexuses undergoes daily circulation within this canal system. An adult person produces an average of 400-450 cc CSF per day and is cleaned from the system with the help of arachnoid villi and leaves its place to newly produced CSF.

The ventricular system consists mainly of the lateral ventricles, the third and fourth ventricles, and the interconnected canal system, also called the fifth ventricle, within the spinal canal. Lateral ventricles open into the 3rd ventricle via foramen monro, 3rd ventricle into the 4th ventricle with aquaductrus cerebri, and 4th ventricle into the spinal canal with the help of obex, foramen magendi and luschkas. disruption may cause enlargement of the ventricles and the appearance of hydrocephalus.

On this canal system, the 3rd ventricle has a special importance in terms of ETV and its anatomy should be well known. The third ventricle can be thought of as a rectangular box; It consists of 4 walls (side walls, front and rear walls), floor and ceiling. The medial surface of the thalamus and the hypothalamus form both lateral walls. Its anterior wall extends from the foramen monro superiorly to the optic chiasm inferiorly. This range includes the fornix, anterior commissure, lamina terminalis, and optic recess. The posterior wall is from the suprapineal recess above to the aquaductus sylvie below. Habenular commissure, pineal body, pineal recess and posterior commissure are located in this wall. The roof extends from the forame monro anteriorly to the suprapineal recess posteriorly. The roof is located just below the body of the Fornix and contains neural tissues, tela choroidea and vascular tissues. The roof lies between the optic recess anteriorly and the aquaductus sylvi posteriorly. The hypothalamus is located anteriorly and the mesencephalon is located posteriorly. structures on the roof; infindibular recess, tuber cinereum, mamillary bodies, posterior perforated substance and anterior part of the tegmentum (7).

Indications

The most well-known and best results of endoscopic third ventriculostomy are undoubtedly aqueduct stenosis and obstructive hydrocephalus. It may be congenital or acquired, secondary to tumor, bleeding or any infection. But it is not limited to obstruction only. ETV is also applied in some communicable hydrocephalus and good results are obtained. It can be used in normal pressure hydrocephalus as well as in posterior fossa tumors, post-infection, myelomeningocele and chiari disease, hydrocephalus developing after intracerebral/intraventricular hemorrhage (8,9).

Idiopathic aqueduct stenosis is a stenosis of the aqueduct between the 3rd ventricle and 4th ventricle, the exact cause of which is unknown. Depending on the stenosis, hydrocephalus appearance is typical in the posterior 3 and lateral ventricles of the stenosis. CSF flow to the 4th ventricle is slowed and this ventricle appears normal or smaller.

Pinela cysts or tumors: Very different tumoral lesions can be seen in the region. The most common tumors are germ cell tumors. They can be examined in two groups as germinomas (most common) and nongerminoma germ cell tumors (NGGCT). Germinomas constitute 65-72% of all germ cell tumors. NGGCTs are endodermal sinus tumor, chorio carcinoma, embryonal cell carcinoma, and teratomas (mature and immature teratomas). Except for mature teratomas, all are malignant lesions. Germ cell tumors can be mixed at a rate of about 10-20% (germinoma+choriocarcinoma; teratoma+endodermal sinus tumor, etc.). In case of simultaneous suprasellar and pineal tumor formation, the diagnosis can be made as germinoma. The second tumoral group is pineal cell lesions and consists of pineasitoma and pineablastomas. Pineal cell lesions constitute 20-30% of tumors in this region. Although pineacytomas are benign lesions, they can show malignant character as a result of different differentiations. The third group consists of other neuroepithelial tumors and especially astrocytic tumors are observed. In this group, a very rare lesion called papillary tumor of the pineal region was described by Jouvet in 2003.

Tectal plate tumors: 10-20% of primary brain tumors in the pediatric population and approximately 1% of adults are located in the brain stem. In the pediatric population, approximately 5% (5) of brain stem tumors and 8% (26) in adults are located in the tectal plate. Tectal plate gliomas are slow-growing, mostly low-grade, focal brainstem gliomas in a critical anatomical location. The narrow passage of colliculus superior, colliculus inferior and aqueductus Sylvii is located in this region. The disease mostly presents with symptoms of increased intracranial pressure due to obstruction of the acuductus Sylvii.

IV. ventricular obstructions. 75% of tumors in this region occur in children. They often emerge from the obex, protrude into the upper cervical canal, and often adapt to the shape of the region into which they have grown. Since

most fourth ventricular ependymomas are seen in the hypoglossal and vagal trigone and adhere to the underlying neural tissue, complete removal of these tumors is difficult in terms of surgical technique. In addition, the tendency to retain the obex makes the complete removal of these tumors almost impossible.

The success rate of ETV decreases in patients with a previous shunt and presenting with shunt dysfunction. However, since ETV is relatively non-invasive in these patients, ETV can be performed after shunt removal if shunt dysfunction is suspected in the patient.

Myelomeningocele cases: It is the most common and the most severe form among congenital defects concerning the spine. Since the early 1980s, it has been declining significantly in industrial countries, thanks to regular prenatal follow-ups and elective terminations. Although the etiology is not known precisely, environmental and genetic factors are thought to be effective. In addition, evidence-based studies show that maternal nutrition has potential importance for spina bifida. In addition, factors such as time of conception, socioeconomic level, and developmental level were indirectly associated with the birth of a child with spina bifida. CDC (Centers for Disease Control and Prevention) in August 1991; As a result of a double-blind, randomized and multicenter study conducted in European countries, it was recommended that mothers with previous affected pregnancies use 5 mg folic acid daily from the moment they plan pregnancy. On the other hand, it was observed that 95% of mothers who gave birth to a child with spina bifida did not have an affected fetus in their previous births. In a double-blind, randomized and multicenter study conducted in Hungary, it was shown that periconceptional folic acid use by the mother significantly reduced the risk of first-time spina bifida. Children with MM are cared for throughout their lives. Closing the sac is just the beginning.

Progressive neurological deterioration caused by shunt dysfunctions, hydro-syringomyelia, stretched spinal cord syndrome, or symptomatic Chiari 2 anomalies should not be excluded. A multidisciplinary approach is required with a team formed by pediatric neurosurgery, orthopedics, urology, physical therapy and rehabilitation specialists. After early surgery, 92% of the patients and 86% of the patients who underwent surgery in their infancy survived in the following 5 years. Death is usually due to Chiari 2 anomaly, restrictive lung diseases due to chest deformity, shunt dysfunctions, and urinary sepsis. 75% of surviving cases have normal intelligence (IQ>80) and 59-60% of shunt dependent cases have normal intelligence

Chiari Type I malformation: The treatment of Chiari type 1 malformation (CM1) and accompanying syringomyelia (SM) cases is surgical and there is no effective medical treatment that can be an alternative to surgical treatment. However, due to the fact that the pathophysiology has not been fully elucidat-

ed and none of the applied methods are successful in all cases, many different surgical methods have been defined, applied and still applied in the historical process. For this reason, the confusion in the literature has increased due to the widespread use of magnetic resonance imaging (MRI) recently, and the diagnosis of asymptomatic or mildly symptomatic cases. It is not clear in the literature which case will be indicated for surgery and which ones can be followed without treatment. Because the true frequency of the disease in the population is not well known, and its natural course has not been clearly demonstrated. Some of these cases have hydrocephalus with or without syringomyelia. ETV is among the options for rescuing these patients from the shunt device.

Dandy-Walker malformation: Dandy-Walker Malformation (DWM) is a developmental anomaly characterized by the presence of a triple neuropathological triad: cystic enlargement of the 4th ventricle, hypoplasia of the cerebellar vermis, and hydrocephalus. The term Dandy-Walker complex used today is; It refers to a group of lesions such as Dandy Walker syndrome (DWS), Dandy-Walker variant and Megasisterna magna. The cause of DWM is still unknown and remains a source of controversy. Generally, it is thought to be caused by atresia of the Magendi and Lushcka foramen, as reported by Dandy-Blackfan, and Taggart-Walker. It is thought that the failure of the foramen magendi to open or the delayed opening during the development period of the 4th ventricle roof causes cystic dilatation of the 4th ventricle with the production of CSF.

There is no specific neurological deficit, usually findings similar to those of infantile hydrocephalus are observed. Clinical findings are seen mainly in the neonatal period (25-30%) and in the first year of life (70-85%). The most common clinical findings; hydrocephalus, cerebellar dysfunction (ataxic gait, nystagmus), increased intracranial pressure (irritability, vomiting, convulsions) and mental retardation. Respiratory failure may develop in the future. Differential diagnosis includes infratentorial arachnoid cyst, other intracranial cystic tumors, hydrocephalus and cerebellar dysplasia. Additional anomalies (50-70%) seen with DWM include central nervous system anomalies such as hydrocephalus, corpus callosum agenesis, agyri, polymicrogyria, syringomyelia, holoprosencephaly and occipital encephalocele, congenital heart disease, neural tube defects, and cleft palate and cleft lip. extracranial anomalies.

ETV can also be used in other types of hydrocephalus such as Postinfectious hydrocephalus, Posthemorrhagic hydrocephalus, Normal pressure hydrocephalus. Close follow-up and treatment of these patients is important.

Although success is not certain after every ETV procedure, the risk taken is worth taking according to the applied procedure. In this respect, the clinic and pathology of these patients should be well established and treatments should be planned accordingly.

Surgical Technique

Knowing the anatomical structure of the brain ventricles, their relationship with other tissues and how they can be seen endoscopically are undoubtedly the most important points in reducing the mortality and morbidity of this operation.

The operation can be performed with navigation or by paying attention to the anatomical landmarks of the skull.

The head of the patient under general anesthesia is fixed in flexion with a spiked cap. Considering the ventricle structure of the patient, the procedure can be performed from the right or left. The right side is mostly preferred for anatomical structures due to habituation. The carlat is passed approximately 3 cm lateral to the midline and the continuation of the midpupillary line, with a linear incision of 3-4 cm crossing the coronal suture. A burr hole is opened approximately 1 cm in front of the coronal suture. The dura is opened and the blunt-ended two-piece trocar of the neuroendoscope is aimed at the midline and sent to the ventricle. By removing the inner part of the trocar, the camera system is advanced and the right lateral ventricle is entered. In the lateral ventricle, the septum pellucidum in the midline, the choroid plexuses extending forward along the midline, the septal vein, and the anterior formen monro are seen. The thalamostriat vein extending laterally on the posterior wall of the foramen monron and the fornix on the anterior wall draw attention. The endoscope is advanced and the 3rd ventricle is entered by passing through the foramen monro. 3. Mamillary bodies at the base of the ventricle are the first anatomical structure that draws attention. The tuber cinereum, extending from just in front of the mammillary bodies to the infindibual recess, is seen as a translucent membrane. Just below this translucent membrane is the basilar artery, and in most people pulsation of the basilar artery is noticeable on the membrane. With the help of a blunt punch and with the help of endoscopic bipolar, this membrane is pierced in front of the basilar artery and the stoma is opened by expanding it with a neuro-balloon catheter. The pre-pontine cistern and its structures can be seen through this hole. If adhesions and membranous structures are observed in the cistern, opening those membranes will increase the success of the operation. The smallest mistake can cause irreversible damage. After the stoma is opened, the endoscope is removed and the operation is terminated (10).

Complications

Intraventricular hemorrhage and neural tissue damage are the leading complications that may occur during ETV. Complications that may occur after surgery have been reported between 0-15%, and death as 1% (8,10,11). When ETV is applied to patients who have undergone shunt

surgery, the complication rate rises up to 30% (12). If we gather the current complications under 4 main headings;

Severe bradycardia,

Neural tissue damage,

Bleeding,

CSF leaks.

Cardiac rhythm disorders: The most important reason is III. surgical manipulations within the ventricle. Endoscope III. Its movements in the ventricle are observed during the perforation of the floor and the inflation stages of the balloon and irrigation. In particular, bradycardia emerges as the most important rhythm disorder. In this case, with the stimulus of anesthesia, the endoscope III. be removed from the ventricle and the balloon deflated.

Because of their anatomical proximity during surgery, the neural structures most prone to trauma are the fornix, hypothalamus, and cranial nerves. Among these, fornix injuries are the most common (4). It rarely causes short-term memory problems. Endoscope III. Damage is observed during the entry and exit of the ventricle or its manipulations in it. Especially the endoscope III. If too much angle is given while removing it from the ventricle, injury will occur.

Success criteria

Some basic criteria will guide us in the evaluation of the post-surgical procedure and in determining our success. The most important of these is the improvement of the patient's clinical symptoms. An objective criterion in patients with open anterior fontanel is relaxation of the fontanel after ETV. In the fundus examination, it can be seen that the papilledema is reduced (12,13). Head circumference measurements are also a guide for us. If we also measure intracranial pressure after ETV, the results obtained from here can show an objective and reliable clinical success or failure. Radiological evaluation, on the other hand, shows the presence of flow from the opened stoma, reduction in ventricular dimensions, and downward springing improvement at the 3th ventricle base guides us in terms of the success of the procedure.

Long term effects

When the reports in the literature that included more than 100 (between 100 and 368) pediatric patients, the success rates were found to be between 48.8% and 89.5%. These series cover many years, but there is no standardization about the mean follow-up times. The follow-up of the patients after ETV is similar to the patients who underwent shunt surgery.

Unlike shunt patients, the reduction in ventricular dimensions progresses in a stable process. If there is no clinical problem, patients should be followed up with annual follow-ups. Although the symptoms of the patients improve quite well, the ventricle sizes may be above normal. The important point is clinical recovery and monitoring the flow from the stoma radiologically. Considering the results of long-term follow-up, endoscopic interventions should be preferred over shunt surgery in appropriate indications due to both the complication rate and the better long-term clinical results.

It is examined in 3 main groups as intraventricular, intracerebral and cortical. Intraventricular hemorrhages are most common in the choroid plexus, veins or III. It occurs after arterial injuries during ventricular floor perforation. If the basilar artery is injured during the sole perforation, the picture may be mortal (12,13).. However, bleeding most commonly occurs from perforating arteries. It should be noted that these arteries are always behind the basilar crest. Therefore, the point where we will pierce the base will always be in front of the basilar crest. However, all radiological examinations should be reviewed in terms of any anatomical variation before surgery and the possibility of a complication should be minimized. If we encounter an intraventricular hemorrhage, first of all it is necessary to remain calm. The endoscope cannula is preserved in its current place and irrigation is started (3). When hemostasis was achieved, the coagulum in the ventricle should be cleaned.

CSF leaks: CSF fistulas and subdural hygromas are complications that can be seen after surgical closure errors. Closing all layers separately and occlusion of the cortical hole with hemostatic agents play an important role in preventing these problems. If a CSF fistula occurs, repeated lumbar punctures are very effective in solving the problem. Neurological deficits can be seen in the early postoperative period. These deficits; Use of cold and nonisotonic fluids in irrigation, sudden changes in intracranial pressure, excessive tension in the hypothalamus due to surgical trauma, subarachnoid hemorrhages, vasospasm and shift of the cerebral parenchyma cause.

Intraventricular bleeding can occur as a result of bleeding from any of the ependymal veins, choroid plexus, basilar artery, or thalamostriate vein.

Due to anatomical proximity, the hypothalamus, thalamus, and fornix may be damaged during ETV. Peroperative cardiac changes may be seen (bradycardia/tachycardia). After hypothalamic damage, diabetes insipidus, weight gain and precociousl puberty can be seen (8,11).

Apart from these, CSF leakage, ventriculitis, subdural fluid accumulation and reclosure of the opened stoma can also be seen.

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CHAPTER 5

CARE AND SPIRITUAL SOCIAL WORK ON THE AXIS OF SPIRITUALITY

Prof. Dr. Fatma DEMİRKAYA MİLOGLU[1]
Assoc.Prof. Gulsah Gundogdu[2] Dr.Koksal Gundogdu[3]
Dr.Seymanur Yılmaz Tascı[4] Dr.Mehmet Emrah YAMAN[5]
Prof.Dr.Yucel KADIOGLU[6]

1 Ataturk University, Faculty of Pharmacy, Analytical Chemistry Department, Turkey.) E-mail:fdkaya@atauni.edu.tr
2 Pamukkale University School of Medicine, Department of Physiology, Turkey E-mail: gdemirkaya81@gmail.com
3 Department of Orthopedics and Traumatology, Denizli State Hospital, Turkey E-mail: koksal_gundogdu@hotmail.com
4 Department of Physiology, Faculty of Medicine, Ataturk University, Turkey E-mail: seymanur34@gmail.com
5 Ataturk University, Faculty of Pharmacy, Analytical Chemistry Department, Turkey.) E-mail: emrahyaman@atauni.edu.tr
6 Ataturk University, Faculty of Pharmacy, Analytical Chemistry Department, Turkey.) E-mail: yucel@atauni.edu.tr

1. Introduction

Osteoarthritis (OA), defined with the cartilage degeneration in joints covered with synovia, joint pain, stiffness and limited mobility, local tenderness, crepitation, and various degrees of inflammation, is the most common chronic degenerative joint disease (Lia Pulsatelli, Olga Addimanda, Veronica Brusi, Branka Pavloska, & Riccardo Meliconi, 2013; Sukur et al., 2016). OA is the most common form of arthritis in the world. Its incidence increases with age, and it usually involves the knee joint, which is called knee OA (KOA) (Johnson & Hunter, 2014). Pain and stiffness are the most obvious symptoms in the joints. (L. Pulsatelli, O. Addimanda, V. Brusi, B. Pavloska, & R. Meliconi, 2013; Sukur et al., 2016). With the increase in the ageing population and obesity worldwide, KOA has become a typical medical problem that affects a large part of society. The main risk factors for the formation of KOA are obesity, age, and gender. OA is becoming a substantial medical and global financial burden due to the increasing world population ageing (Johnson & Hunter, 2014). Nowadays, diagnosis of OA, which causes socioeconomic losses, is crucial. KOA is a metabolically active and dynamic process triggered by biochemical and mechanical factors, and in this process, repair with destruction occur together. In KOA, both joint cartilage and subchondral bone processes (e.g., osteophyte, eburnation, sclerosis, subchondral cyst, and synovial inflammation) are observed. Tissue damage occurs due to the disturbance between matrix construction and destruction in KOA. In the catabolic process, which includes reduced matrix synthesis, increased proteinase activity, and chondrocyte apoptosis, cartilage destruction increases as a result of cytokines released from the synovium, chondrocytes, and inflammatory mediators with morphological, biochemical, and molecular changes (Chauffier et al., 2012; Takaishi, Kimura, Dalal, Okada, & D'Armiento, 2008).

However, the pathophysiology of OA is still not thoroughly investigated (Conde et al., 2011). Presently, the diagnosis of KOA is usually evaluated through clinical and radiological findings, according to the criteria of American College of Rheumatology (ACR) (Kawasaki, Inoue, Ushiyama, & Fukuda, 1998). Disease's severity is determined with The Kellgren Lawrence (KL) score (Kellgren & Lawrence, 1957) radiographically. However, new biomarkers and parameters for the diagnosis and treatment of the disease have begun to be emphasized in recent years, as the disease can be diagnosed after pathologic findings have occurred. Recently, identifying biomarkers that can provide early diagnosis of the disease has become the focus of researchers, and which molecule or molecules can be used in diagnosis have been emphasized (Z.-G. Li et al., 2012; Poonpet & Honsawek, 2014). Adipose tissue-derived adipokines have a significant

effect on cartilage and bone homeostasis. The relationship between KOA and adipokines has been discussed in several studies (Cakir, Ozcan, Korkmaz, & Durusoy, 2019; Gundogdu & Gundogdu, 2018; Gundogdu, Gundogdu, Miloglu, & Tascı, 2019). As adipokines have been considered essential mediators that provide an inflammatory connection in OA, they have become the focus of attention in studies on the pathophysiology of KOA (Z.-G. Li et al., 2012; Poonpet & Honsawek, 2014).

Preptin, a recently isolated peptide hormone composed of 34 amino acids blessed with amylin and insulin from beta cells of the pancreas, occurred as a regulatory compound in bone metabolism (BUCHANAN, PHILLIPS, & COOPER, 2001). The administration of preptin was found to increase the bone area and mineralizing surface in adult mice and contribute to bone anabolism (N. Li et al., 2013). It has been reported that preptin stimulates osteoblast proliferation and inhibit osteoblast apoptosis (Wong, Baldock, & Herzog, 2010). Previous studies have reported that preptin plays a role in the etiopathology of different diseases, such as obesity, diabetes, polycystic ovary syndrome, osteopenia, and osteoporosis (Baykus et al., 2012; Wallis, 2009). The serum preptin level could be associated with inflammation and bone health (Yan et al., 2011).

Irisin is a new adipokine and myokine secreted into circulation (Boström et al., 2012). It is released by the proteolytic cleavage of fibronectin type III, the precursor of irisin. Irisin accelerates the conversion of white adipose tissue to brown adipose tissue by enhancing the main action of UCP1. It is found in many tissues, and it has many effects on the tissues it contains (Mahgoub, D'Souza, Al Darmaki, Baniyas, & Adeghate, 2018). İrisin is stimulated by exercise in mice and humans, and slightly increased irisin levels in the blood causing increased energy consumption in mice without any change in movement or food intake (Boström et al., 2012). Studies have demonstrated that irisin is involved in metabolic diseases, ageing, cardiovascular diseases, inflammation, and neurogenesis (Mahgoub et al., 2018; Polyzos et al., 2018). Moreover, irisin has antioxidant and anti-inflammatory effects and a protective effect on bone tissue (Mahgoub et al., 2018).

Despite the literature has shown a relationship between KOA and adipokines, only two studies have been conducted on preptin and irisin thus far. The first study has determined that the preptin level decreased in female patients with KOA (Cakir et al., 2019). The second has determined that serum irisin levels correlate with the severity of KOA (Mao, Xu, Xie, & Dong, 2016).

This study aimed to determine serum preptin and irisin levels using the ELISA method and investigate the relationship between serum preptin and irisin levels and the various laboratory parameters in KOA.

2. Materials and Methods

Subjects

Eighty patients aged 45–75 years who applied to the Erzurum Regional Training and Research Hospital and were diagnosed with KOA according to the diagnostic criteria of KOA made by the American Rheumatism Association (Kawasaki et al., 1998) between June 2018 and November 2018 were included in the study as the patient group. The healthy controls (HCs) consisted of 30 healthy individuals in the same age group who applied to the same orthopedic clinic. Samples (blood) were obtained from HCs and KOA patients at the time of admission to the hospital following 12 h of fasting. All participants underwent anteroposterior knee X-ray radiographs with weight-bearing and were evaluated by the same orthopedist.

KOA Exclusion Criteria

- Patients who have rheumatic diseases, such as traumatic, suppurative, and rheumatoid arthritis (RA)
- Patients with metabolic diseases
- Patients who had undergone arthroscopic knee surgery within the last six months and hip OA
- Patients who have had a bilateral or unilateral knee replacement
- Patients who have knee joint trauma and glucocorticoid and/or steroid hormone use experience

Laboratory Parameters

The C reactive protein (CRP) concentration (mg/dL), erythrocyte/sedimentation ratio (ESR, mm/h), white blood cell (WBC), lymphocyte (K/μL), neutrophil (K/μL), thrombocyte (K/μL), monocyte counts (K/uL), and platelet (K/μL) were considered as routine blood parameters in both groups. Using these data, the platelet/lymphocyte ratio (PLR) and blood neutrophil/lymphocyte ratio (NLR) were determined. The remaining samples were collected for preptin and irisin analysis by ELISA and centrifuged at 1500 g for 10 min; the serum samples were separated and kept at −80°C until analysis.

Radiological Evaluation

Anteroposterior knee radiographs were requested from both the patients and HCs on admission to the hospital. The radiographs were analyzed by an orthopedist and graded using the KL score criteria as follows (Kellgren & Lawrence, 1957):

Grade 0: No evidence of OA

Grade 1: Suspicious narrowing of joint space and possible osteophyte formation

Grade 2: Specific osteophyte with possible narrowing of joint space

Grade 3: Multiple osteophytes, precise narrowing of joint space, maybe sclerosis and bone deformation

Grade 4: Large osteophytes, severe narrowing of joint space, severe sclerosis, and marked deformities in bone margins

The knee charts of the KOA group were classified according to the KL grading system (**Figure 1)**. Grades 1–3 were classified as mild-to-moderate KOA patients (45 patients) and Grade 4 as severe KOA patients (35 patients). Aside from these groups, the sample was also divided into two groups, including KOA patients and HCs.

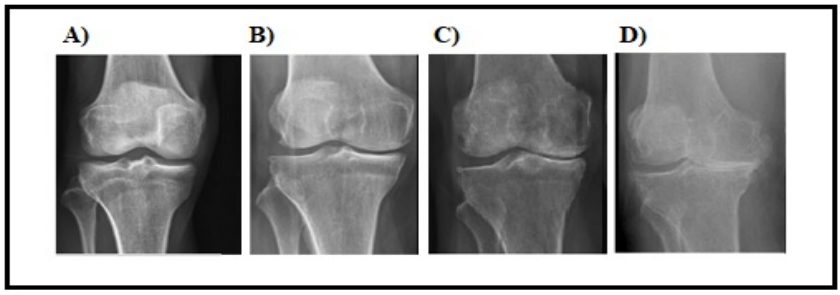

Figure 1. *Knee radiographic image of the KOA patients according to KL grading;* ***(A)*** *Grade 1,* ***(B)*** *Grade 2,* ***(C)*** *Grade 3,* ***(D)*** *Grade 4.*

ELISA Method for Determining Serum Preptin and Irisin Levels

Ultraviolet-Visible spectrophotometer (A Multiscan GO 51119300 model, Thermo Scientific, Massachusetts, USA) and 96-well ELISA kits (Elabscience, China) were used to determine the preptin and irisin levels in the obtained serum samples according to the producer's instructions.

Statistical analysis

All statistical analyses of the study were carried out with SPSS version 20. The demographic and biochemical parameters of the KOA patients and HCs were evaluated using descriptive statistical analysis. An independent *samples t-test* was used to compare the KL scores of the KOA patients. The correlations between the preptin and irisin levels and the biochemical parameters of the KOA patients and HC's were determined using Pearson's-correlation analysis.The mean±standard deviation (SD) was given for obtained all results, and statistical significance was accepted with a P value < 0.05.

3. Results

Demographic features of KOA patients and HCs

Eighty KOA patients and 40 HCs were evaluated. **Table 1** summarizes the demographic parameters of the participants. No statistically significant variations were found between the KOA patients and HCs in gender, age, and body mass index (BMI) ($P > 0.05$). Thus, all demographic data were matched.

Table 1. *The demographic features of KOA patients and HC's*

Demographic Features	KOA patients (n:80) Mean ±SD	HC's (n:30) Mean ±SD	p[a]
Age (Years)	56.2±6.14	52.6±13.03	0.091
Gender (% Female)	83.8	73.3	0.216
BMI	30.8±4.14	28.9±5.05	0.066

*[a]: independent samples t-test * p <0.05 is significant, SD: standard deviation, BMI: Body Mass Index, KOA: Knee osteoarthritis, HC: healthy control individuals.*

Laboratory features of KOA patients and HCs

The hemogram parameters were examined in the KOA patients and HCs (**Table 2**). Whereas the neutrophil count (K/uL) of the KOA patients was significantly lower ($P = 0.045$) than that of the HCs, the PLR value of the KOA patients was significantly higher ($P = 0.022$) than that of the HCs. No significant difference was found in other hemogram parameters ($P > 0.05$). The ESR was significantly higher in the KOA patients than in the HCs ($P = 0.001$). The mean WBC and CRP values were similar in both groups ($P > 0.05$).

Table 2. *Comparison of laboratory features between KOA patients and HC's*

Laboratory Features	KOA patients (n:80) mean ±SD	HC's (n:30) mean ±SD	p[a]
WBC	8.27±2.16	8.05±2.20	0.657
ESR (mm/h)	13.17±7.94	7.90±4.45	**0.001***
CRP (mg/dL)	1.06±1.77	0.43±0.29	0.057
Platelet count (K/uL)	277.18±52.18	260.89±51.49	0.175
Neutrophil count (K/uL)	4.20±1.47	4.95±1.79	**0.045***
Lymphocyte count (K/uL)	2.39±0.44	2.27±0.64	0.369
Monocyte count (K/uL)	0.49±0.19	0.48±0.14	0.749
PLR	133.13±51.03	110.41±19.01	**0.022***
NLR	2.03±1.04	2.18±1.16	0.529

*[a]:independent samples t-test * p <0.05 is significant, SD: standard deviation, BMI: Body Mass Index, KOA: Knee osteoarthritis, HC: healthy control individuals. WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio.*

Serum Preptin and Irisin levels of KOA patients and HCs

***For Preptin*:** The preptin levels were determined using the UV absorbance values measured at 450 nm. The calibration curves obtained by plotting the A_{450} values versus the concentration showed linear relationships. The curves showed good linearity, and the regression equation and correlation coefficient (R^2) were Ap = 0.0006Cp + 0.0661 and 0.9936 at the 0–4000 pg/mL concentration range of preptin, respectively (Cp: preptin concentration (pg/mL); Ap: preptin absorbance).

The serum preptin levels were lower in the KOA patients than in the HCs. The preptin levels of the KOA patients and HCs were 403.18 ± 78.24 pg/mL and 422.95 ± 101.08 pg/mL, respectively ($P > 0.05$) (**Figure 2A**). When the serum preptin level was evaluated according to the KL score, a statistically significant decrease was found in the severe-KOA patients compared with the mild to moderate-KOA patients. The preptin levels in the severe and mild-to-moderate KOA patients were found as 344.15 ± 38.80 pg/mL and 416.48 ± 75.35 pg/mL, respectively (**Figure 2B**). **Figure 2C** shows the absorption spectra of preptin in severe KOA patients, mild to moderate KOA patients, and HCs.

Pearson's correlation analysis evaluated the relationship between the BMI, WBC, and CRP values and the serum preptin levels in the KOA patients. There was no statistically significant correlation between the serum preptin levels and the BMI or WBC values (r = −0.095, $P = 0.471$, r = −0.188, $P = 0.182$, respectively) (**Figure 2D and 2E**). However, a statistically significant negative correlation was observed between the serum preptin levels and CRP (r = −0.286, $P = 0.040$) (**Figure 2F**).

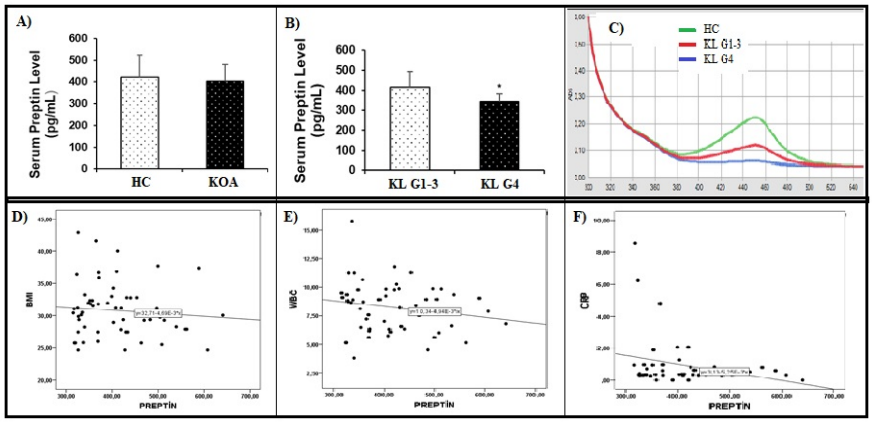

Figure 2.

A) *Serum preptin levels of KOA patients vs HCs*

B) *Serum preptin levels of mild-moderate KOA vs severe KOA patients*

C) *Preptin absorption spectra of severe KOA patients, mild-moderate KOA patients and HCs*

D) *Negative correlation between serum preptin levels with BMI value in KOA patients (p>0.05) with Pearson's Correlation Scatter*

E) *Negative correlation between serum preptin levels with WBC value in KOA patients (p>0.05) with Pearson's Correlation Scatter*

F) *Statistically significant negative correlation between serum preptin levels with CRP value in KOA patients (p<0.05) with Pearson's-Correlation Scatter*

*(KOA: Knee osteoarthritis, HC: healthy control individual *: Statistically significance in patients with severe KOA patients compared with mild-to-moderate KOA patients, p <0.01*

***For Irisin*:** The irisin levels were also determined using the UV absorbance values measured at 450 nm. The calibration curves were plotted the A450 values versus the irisin concentration. Irisin exhibited good linearity at a serum irisin concentration range of 0–10 ng/mL. A regression equation of the absorbance of irisin was determined as A = 0.244Ci + 0.0745 (R^2 = 0.9745) by the least-squares method, where Ci is the concentration (ng/mL) of irisin, A is the absorbance of irisin, and R is the correlation coefficient of serum. The serum irisin levels were lower in the KOA groups than in the HCs. The irisin levels of the KOA patients and HCs were 6.52 ± 2.01 ng/mL and 8.41 ± 2.05 ng/mL, respectively ($P < 0.001$) (**Figure 3A**). When the serum irisin level was evaluated according to the KL score, a statistically significant decrease was found in the serum irisin level of the severe KOA patients compared with the mild-to-moderate KOA patients. The irisin levels of the severe and mild-to-moderate KOA patients were 4.62 ± 1.28 ng/mL and 7.87 ± 1.13 ng/mL, $P < 0.01$), respectively **(Figure 3B**). **Figure 3C** shows the absorption spectra of preptin in the severe KOA patients, mild-to-moderate KOA patients, and HCs.

Pearson's correlation analysis evaluated the relationship between the BMI, WBC, and CRP values and the serum irisin levels of the KOA patients. Whereas no significant correlation was found between the serum irisin levels and the WBC values (r = −0.066, $P = 0.641$) (**Figure 3D**), the serum irisin levels were statistically significantly negatively correlated with BMI and CRP (r = −0.321, $P = 0.012$, r = −0.396, $P = 0.004$, respectively) (**Figure 3E and 3F**).

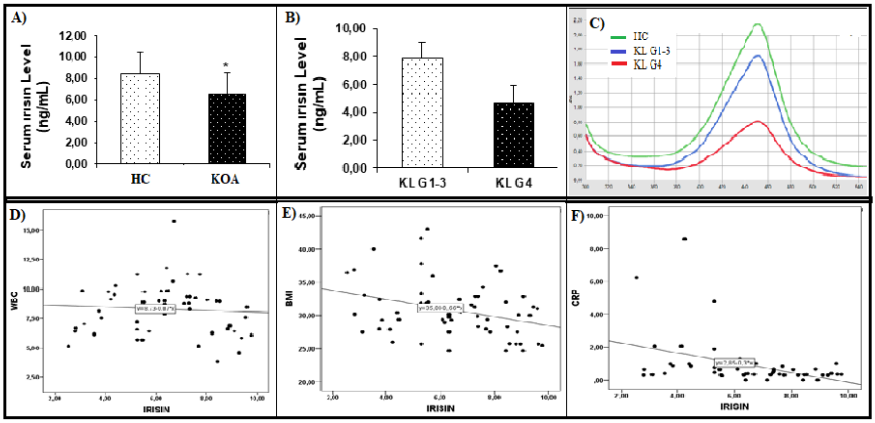

Figure 3.

A) *Serum irisin levels of KOA patients vs HCs*

B) *Mild-moderate of KOA vs severe KOA patients*

C) *Irisin absorption spectra of severe KOA patients, mild-moderate KOA patients and HCs*

D) *Negative Correlation between serum irisin levels with WBC value in KOA patients (p>0.05) with Pearson's Correlation Scatter*

E) *Statistically significant negative correlation between serum irisin levels with BMI value in KOA patients (p<0.05) with Pearson's Correlation Scatter*

F) *Statistically significant negative correlation between serum irisin levels with CRP value in KOA patients (p<0.05) with Pearson's-Correlation Scatter*

*(KOA: Knee osteoarthritis, HC: healthy control individual *: Statistically significance in patients with severe KOA patients compared with mild-to-moderate KOA patients, p <0.01.*

4. Discussion

KOA is a degenerative joint disease that affects all joints and tissues around the knee joint and is characterized by cartilage destruction and changes in the subchondral bone. KOA has become a primary health problem because of its increasing incidence (Johnson & Hunter, 2014). Although many risk factors are mentioned in the aetiology of KOA, its pathophysiology is still not fully explained (Conde et al., 2011). KOA has become a serious problem in recent years because of the increase in obesity and the ageing population (Johnson & Hunter, 2014), but there are no laboratory findings specific for KOA yet. Therefore, the early diagnosis of this disease is crucial because it causes socioeconomic losses. Currently, the diagnosis of KOA is made according to the ACR criteria (Kawasaki et al., 1998). At the same time, the KL radiographic score is used to determine the degree of KOA (Kellgren & Lawrence, 1957). KOA can be detected after the destruction of the articular cartilage and by pathological

changes in the synovial fluid, along with clinical and radiological findings (Johnson & Hunter, 2014). The discovery of new biomarkers to obtain the early diagnosis of the disease has become the focus of researchers, and which molecule or molecules can be used in diagnosis have been investigated. Although OA is known to be a non-inflammatory disease, recent studies have indicated that a low grade has a significant effect on the pathophysiology of the disease (Gundogdu & Gundogdu, 2018; Gundogdu et al., 2019; Johnson & Hunter, 2014).

Tissue damage occurs due to the imbalance between matrix construction and destruction in KOA. The catabolic process, which includes decreased matrix synthesis, increased proteinase activity, and chondrocyte apoptosis, causes morphological, biochemical, and molecular changes. Moreover, cartilage destruction increases by inducing cytokines, such as TNF-α, IL-6, and IL-1β which are released from the synovium and chondrocytes, and the synthesis of metalloproteinases and inflammatory chemokines (Goldring & Otero, 2011; Gundogdu et al., 2020). Reactive oxygen species (ROS) play a vital role in both cartilage degradation and inflammation seen in KOA. ROS cause DNA damage in articular cartilage; the oxidation of carbohydrates, proteins, and lipids; and oxidative damage to cellular proteins (Davies, Guilak, Weinberg, & Fermor, 2008; Fermor et al., 2007). As a result of the ageing population and the increase in obesity worldwide, OA is considered a vast health problem that will soon affect a large part of society and become a considerable medical and financial burden in the world budget (Di Cesare P.E., 2006; Johnson & Hunter, 2014).

Adipokines born of adipose tissue have an important place in bone homeostasis and cartilage. This is why adipokines have become the focus of attention in recent studies on KOA pathophysiology (de Boer et al., 2012; Gundogdu & Gundogdu, 2018; Gundogdu et al., 2019). Irisin, a new adipokine, is released by proteolytic cleavage of its precursor, fibronectin type III (Boström et al., 2012). Irisin, which is found in many tissues, has been determined to have antioxidant, anti-inflammatory, osteoblastic, and protective effects on bone tissue. It also plays a role in various metabolic diseases involved in energy homeostasis, ageing, inflammation, and cardiovascular diseases (Mahgoub et al., 2018; A. I. Mazur-Bialy, Pochec, & Zarawski, 2017). Moreover, it is considered to have an anti-inflammatory effect (Dulian et al., 2015). Mazur-Bialy et al. (A. I. Mazur-Bialy et al., 2017). showed that treating lipopolysaccharide-stimulated macrophages with low irisin concentrations reduces their inflammatory activity and decreases the release and expression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β. In another study by Mazur-Bialy et al. (Agnieszka Irena Mazur-Bialy, 2017), irisin was found to have an anti-inflammatory effect because it reduces ROS production and thus modulates macrophage activity.

Preptin, one of the other adipokines examined in the present study, is a peptide with 34 amino acids secreted from pancreatic B-cells, together with insulin and amylin. Preptin increases the insulin secretion hormone and has an anabolic effect on bone synergistically with insulin (BUCHANAN et al., 2001). Preptin has an enhancing effect on osteoblasts and osteoclasts' cell differentiation and activity (Wong et al., 2010). Moreover, low bone mineral densities are associated with low circulating preptin levels in patients with osteoporosis and osteopenia (N. Li et al., 2013). Preptin plays a role in the etiopathology of various diseases, including obesity, PCOS, diabetes, osteoporosis, and osteopenia (Baykus et al., 2012; N. Li et al., 2013; Wallis, 2009). Nazari et al. showed that the serum preptin level decreased in postmenopausal women compared with premenopausal women. There was a positive correlation between the serum preptin level and femoral and total hip bone mineral density (Nazari et al., 2018).

In light of this information, the present study hypothesized that serum preptin and irisin levels decreased in KOA patients. The severity of the disease was correlated with the decrease in serum preptin and irisin levels. Accordingly, the serum preptin and irisin levels were examined using the ELISA method in serum samples taken from 80 KOA patients and 30 HCs. The severity of the disease was determined using knee radiographs. The hemogram and biochemical parameters were recorded, and the inflammatory relationship of the disease was demonstrated. Çakır et al. (Cakir et al., 2019) observed that the preptin levels, which are known to have anabolic effects on bone metabolism, decreased in patients with KOA compared with the HCs. Similarly, in the present study, the serum preptin levels were determined using the ELISA method in KOA patients and HCs. The preptin levels of KOA patients decreased compared with that of HCs. However, the decrease in our study was not statistically significant (**Figure 2A**). In the evaluation according to the KL score, the decrease in the serum preptin levels was statistically significant in patients with severe KOA compared with those with mild-to-moderate KOA (**Figure 2B**). The relationship between C-reactive protein (CRP), a marker of systemic inflammation, and OA has been shown in various studies, but its association with disease findings have been conflicting (Jin et al., 2015). In this study, the serum preptin levels and laboratory parameters, a significant negative correlation was found in the CRP value (**Figure 2F**).

Mao et al. (Mao et al., 2016) reported that irisin levels in the serum and synovial fluid decreased in KOA patients and were correlated with disease severity. Similarly, in the current study, the serum irisin levels were determined using the ELISA method in KOA patients and HCs. The irisin levels of KOA patients significantly decreased compared with HCs **(Figure 3A**). In the evaluation according to the KL score, a significant decrease was detected in the serum irisin levels of severe KOA patients compared

with mild-to-moderate KOA patients (**Figure 3B**). In examining the relationship between the serum irisin level and the laboratory parameters, a negative correlation was found between the serum irisin level and the BMI and CRP values (**Figures 3E–3F**).

In conclusion, this study showed that the serum preptin and irisin levels determined by the ELISA method decreased in KOA patients compared with the HCs. This result provides a new perspective on the relationship between serum preptin and irisin levels and KOA. This decrease in ırisin can be especially a potential marker in early-stage KOA patients. If further studies involving more participants are conducted, the serum level may guide clinicians, as it can serve as a new parameter in the early diagnosis of patients with KOA.

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CHAPTER 6

SIRT1 AND DIABETES MELLITUS

Nilüfer AKGÜN ÜNAL[1], Ömer ÜNAL[2]

1 Ondokuz Mayıs University, Medicine Faculty, Department of Biophysics A.D., Samsun, Turkey, nilüfer.akgununal@omu.edu.tr , ORCID: 0000-0001-7750-482X
2 Selcuk University, Medicine Faculty, Department of Physiology, Konya, Turkey omerunal@selcuk.edu.tr ORCID: 0000-0002-4816-830X

1. INTRODUCTION

The physiopathological mechanisms of diabetes are multifactorial and play a very important role in the development of metabolic disorder. Therefore, there are efforts to develop dietary strategies to counter the oxidative stress caused by diabetes and its possible side effects on cardiovascular diseases. Resveratrol is a potential candidate for the treatment of cardiovascular diseases due to its protective antioxidant, anti-inflammatory and anti-angiogenic properties. In animal model experiments conducted in recent years, resveratrol has been used as an effective activator for Sirtuin 1 (SIRT1) and it has been found that resveratrol has beneficial effects by increasing the activation of SIRT1 (Table 1). Consequently, there is increasing interest in the relationship between SIRT1 and diabetes. Emerging evidence has shown that mitochondrial changes may be a central mediator for pathological processes in diabetes. Therefore, the search for appropriate therapeutic approaches to target mitochondrial dysfunction also offers a future for the management of diabetes. The purpose of the present review is to interpret the relationship between SIRT1 and diabetes with dietary strategies.

Table 1. Role of sirtuin 1 on glucose/lipid metabolism (Kitada & Koya, 2013).

Pancreas	Insulin secretion ↑ β-Cell protection ↑
Insulin signaling	Insulin sensitivity ↑
Inflammation	Insulin sensitivity ↑
Adipose tissue	Lipid mobilization↑ Adiponectin↑
Skeletal muscle	Mitochondria biogenesis ↑ Glucose uptake ↑
Mitochondria	Biogenesis ↑ ROS ↓ Fatty acid oxidation ↑
Liver	Glucose/Lipid metabolism
	Glucose production
	Fatty acid oxidation ↑
Circadian rhythm	Glucose/Lipid metabolism

DNA tightly translated by histone proteins is impossible to transcribe, and histone acetylation is an important regulatory mechanism during transcription. Histone deacetylation enzymes allow transcription by cleaving DNA from the histone complex. Sirtuin proteins were originally identified by researchers as gene regulators by deacetylation of histone or nonhistone targets in yeast. Sirtuins require the nicotinamide adenine dinucleotide (NAD+) cofactor and are in the histone deacetylase (HDAC) type III class. They are not similar to HDACs, but they have different substrates, from metabolic enzymes such as histones to structural proteins (Bagul, Deepthi, Sultana, & Banerjee, 2015).

SIRT1 is one of seven mammalian homologues (SIRT1 – SIRT7) of yeast silent information regulator 2 (Sir2), the first SIRT family member discovered, and still the most studied, as it is a potential target specifically for treating cardiovascular diseases (Karbasforooshan & Karimi, 2017).

SIRT1 is a NAD^+ dependent protein deacetylase (Kang et al., 2017) and it plays many roles in cellular metabolism (Blander & Guarente, 2004). As an important protein deacetylase, the regulatory effect of SIRT1 on mitochondrial dynamics has received considerable attention. Diabetic cardiomyopathy, one of the cardiovascular diseases, is recognized as a potential target for the treatment of human pathologies (S. Guo et al., 2015; Pillarisetti, 2008; Sulaiman et al., 2010) and targeting SIRT1 for preventing angiocardiopathy, one of the important side effects of diabetes, has numerous benefits. further revealed by the findings (Ding et al., 2015; S. Zhou et al., 2011). In experimental studies, it has been reported that the reduced SIRT1 signaling pathway significantly impairs myocardial ischemia/reperfusion injury in both type 1 and type 2 diabetes models, and by stimulating SIRT1 with melatonin administration, it significantly reduces the damage by preventing oxidative stress and apoptosis (Yu et al., 2015; D. Zhang et al., 2018).

In the studies, it is still not fully known whether the effect of SIRT1 especially on mitochondrial dynamics is effective in the pathological process of diabetic cardiomyopathy. In one study, SIRT1 was found to cause diabetic cardiomyopathy by causing phenotypes resembling diabetic cardiomyopathy in the heart of knockout mice. SIRT1, activated by resveratrol administration, has been observed to improve impaired cardiac function and mitochondrial biogenesis in mice with diabetic cardiomyopathy (Ma et al., 2017). All this evidence suggests that targeting SIRT1 may be a promising therapeutic strategy for diabetic cardiomyopathy.

2. SIRT1 AND PGC-1α

Peroxisome proliferator - activated receptor gamma coactivator (PGC) -1 alpha (PGC-1α) is a transcriptional co-activator of SIRT1 signaling, which plays an important role in the regulation of genes involved in heart muscle metabolism, disturbance of mitochondrial dynamics and contraction in heart muscle (Koka, Aluri, Xi, Lesnefsky, & Kukreja, 2014). When cellular energy stores decrease, the level of NAD increases and this activates SIRT1. Next, SIRT1 inactivates PGC-1α, thereby increasing ATP formation (Scarpulla, 2011). It can also be activated by 2 key cellular metabolic sensors, AMPK (5'-adenosine monophosphate-activated protein kinase) or SIRT1, via direct phosphorylation or deacetylation, respectively (Koka et al., 2014). Studies show that SIRT1 increases PGC-1α activity when interacting with physically deacetylated PGC-1α (Ma et al., 2017). It has also been observed that SIRT1 improves mitochondrial dynamics through deacetylation of PGC-1α and regulation of proteins (Ma et al., 2017).

3. RESVERATROL METABOLISM

Resveratrol (trans-3,5,4'-trihydroxyl stilbene) is a plant-derived polyphenol that is frequently produced in plants exposed to many environmental stresses (Pallàs, Porquet, Vicente, & Sanfeliu, 2013). Resveratrol exists in two forms, with effects on different biological tissues. It is known that trans resveratrol is a non-toxic and effective polyphenol and is frequently studied (Pallàs et al., 2013). Resveratrol is found in the outer peel of grapes, rasp berries, blue berries, peanuts, some pine trees and medicinal plants such as Polygonum capsidatum (Allard, Perez, Zou, & de Cabo, 2009). Resveratrol attracts great attention with its protective effects in different pathological conditions (Smoliga, Baur, & Hausenblas, 2011). The most important of these have numerous effects such as antioxidant, anti-platelet, lipid peroxidation inhibitor, vasodilator, anti-inflammatory, anti-cancer, anti-mutagen and cardioprotective (Smoliga et al., 2011). Among these positive effects of resveratrol are antioxidant capacity, proteins associated with survival signals, enzyme secretion levels, activities and regulation of ion channels (Baur & Sinclair, 2006; Kwon, Kim, Shin, & Han, 2010). The protective effects of resveratrol are generally due to its oxidative stress reducing properties. Like most polyphenols, resveratrol has an intrinsic antioxidant capacity and stimulates the expression of many antioxidant enzymes (Halliwell, 2007; Robb, Winkelmolen, Visanji, Brotchie, & Stuart, 2008). At the same time, studies show that the poor bioavailability of resveratrol and its low ability to capture ROS are not dependent on direct reactions in the regulation of cellular mechanisms (Leonard et al., 2003; Sale et al., 2004). The important effects of resveratrol are related to the protection of the cell against oxidative stress-induced death, and by initiating a cascade system related to intracellular events, it causes the stimulation of cellular defense systems (Pallàs et al., 2013; Robb et al., 2008).

When the responses of resveratrol treatment on different tissues were evaluated, it was shown that resveratrol stimulated the activities of intracellular signaling molecules (such as sirtuins and AMPKs) that regulate metabolism in many tissues (Baur & Sinclair, 2006). At the same time, many metabolites have the ability to stimulate SIRT1 and inhibit cyclooxygenase when administered onto tissue (Baur & Sinclair, 2006). Although 21 different molecules have been identified as activators of SIRT1, resveratrol has attracted the most attention (Howitz et al., 2003). It has also been shown that resveratrol significantly increases SIRT1 activity through an allosteric interaction, resulting in increased SIRT1 affinity for both NAD^+ and acetylated substrate (Howitz et al., 2003; Jang et al., 1997). Due to its protective properties, resveratrol is an important candidate for the treatment of cardiovascular diseases (Das & Das, 2007). Studies have found that resveratrol has significant and beneficial effects by increasing

the activation of SIRT1 (Baur, Ungvari, Minor, Le Couteur, & de Cabo, 2012; Côté et al., 2015). In addition, it has been shown that resveratrol increases life expectancy by more than 60% by stimulating the sirtuins (Valenzano & Cellerino, 2006; Wood et al., 2004).

4. RESVERATROL AND DIABETES MELLITUS

Resveratrol is a polyphenolic flavonoid with pleiotropic activities that exert different beneficial effects depending on SIRT1 to slow or inhibit the progression of many diseases (including diabetes and cardiovascular diseases) (Hung, Chen, Huang, Lee, & Su, 2000; Ignatowicz & Baer-Dubowska, 2001). In recent years, the effects of resveratrol on diabetes have been frequently studied in various animal models. The results show that resveratrol significantly treats diabetes by stimulating many mechanisms in diabetic animals (Szkudelska & Szkudelski, 2010; Szkudelski & Szkudelska, 2011; Vang et al., 2011). Antihyperglycemic effect of resveratrol, especially in type 1 diabetic animals; The increase in blood insulin levels is due to the inhibition of hepatic glucose output and the increase in peripheral glucose utilization (Szkudelski & Szkudelska, 2015). It has also been shown that resveratrol treats cardiac failure and atherosclerosis by preventing it (Bertelli & Das, 2009; Das & Das, 2007). It has been reported that resveratrol administration reduces infarct size and apoptosis rate by increasing antioxidant proteins in diabetic rat heart (Dekkers et al., 2008; Thirunavukkarasu et al., 2007). In another study, it was reported that resveratrol (2.5 mg/kg/day orally) administration increased GLUT4 translocation and glucose uptake in diabetic rat myocardium (Penumathsa et al., 2008). In addition, resveratrol (20 mg/kg/day orally) treatment improves left ventricular (LV) diastolic relaxation by reducing oxidative/nitrosative stress (H. Zhang et al., 2010), while 2.5 mg/kg daily resveratrol treatment reduces ventricular inflammation and remodeling. It has been shown to improve diabetic heart function by reducing the amount of diabetes (Delucchi et al., 2012). In addition, resveratrol has been shown to increase cardiac autophagy in diabetic cardiomyopathy and during ischemia-reperfusion or hypoxia-reoxygenation (Gurusamy et al., 2010).

In a study, it was reported that resveratrol regulates mitochondrial ROS homeostasis through increased SOD2 activity and PGC-1α expression (X. Zhou et al., 2014). Resveratrol has been shown to improve cardiac oxidative stress, mitochondrial dysfunction and myocardial fibrosis caused by diabetes (Bagul, Deepthi, et al., 2015; R. Guo et al., 2015; Mohammadshahi, Haidari, & Soufi, 2014). Oxidative stress, mitochondrial dysfunction, SIRT1-mediated PGC-1α deacetylation caused by diabetes in myocardial tissues or cardiomyocytes are inhibited by resveratrol administration, therefore resveratrol-supported therapeutic applications have been suggested in patients with diabetic cardiomyopathy (Fang et al., 2018).

5. RESVERATROL AND SIRT1

Sirtuins, which mediate the deacetylation of proteins, have been found to have important regulatory effects for some cellular processes. DNA repair, energy homeostasis control, redox balance, anti-aging and insulin secretion are some important biological functions mediated by sirtuins (Shoba et al., 2009). Studies have shown that protein expression of type 1 diabetes and mRNA analyzes of sirtuins have down-regulated expression of all sirtuins. In another study, resveratrol administration due to cardiac complication pathology decreased the downregulation expression of SIRT1, SIRT2, SIRT3 and SIRT5. In addition, in the case of T2DM, SIRT1 expression decreased and SIRT3 expression increased without any change in other sirtuins in the diabetic heart, and resveratrol administration caused SIRT1 expression to return to normal (Bagul, Dinda, & Banerjee, 2015).

Molecules that stimulate SIRT1 are important therapeutic potentials for ameliorating metabolic changes. Beneficial effects of resveratrol have been demonstrated by increased expression of SIRT1 or by treatment with the SIRT1 activator SIRT1720 (Feige et al., 2008). Inhibited enzymatic activity of SIRT1 has been found to suppress SERCA2a in diabetes, and it has been reported that resveratrol administration activated SIRT1 to restore SERCA2a expression and cardiac function to normal values in diabetic mice. As a result, it was observed that SIRT1 acts as an activator of SERCA2 gene expression of cardiomyocytes with increased glucose (Sulaiman et al., 2010). In addition, considering that SIRT1 is expressed in the central nervous system, it is assumed that the antidiabetic effects of resveratrol are also mediated by the brain in animal model studies.

These activities of SIRT1 mentioned above; p53 binds to histone proteins in addition to PGC-1α and some transcription factors including the FOXO family and metabolic regulators. In addition, it increases glucose uptake into the cell by stimulating the GLUT4 gene (glucose transporter) (Michael et al., 2001). Resveratrol inhibits the aging-induced decrease in the cardiovascular mechanism by stimulating the expression of some different genes (such as SIRT1, SIRT2, SIRT4, FOXO1, FOXO3a). PGC-1α also increases glucose uptake by stimulating the expression of the insulin-sensitive glucose transporter GLUT4 gene (Michael et al., 2001). SIRT1 level also increases in a dose-dependent manner in endothelial cells treated with resveratrol (Kao et al., 2010). In a study conducted in human coronary arterial endothelial cells, when mitochondrial ROS production was tested, it was shown that although resveratrol increased the amount of GSH by regulating MnSOD expression, these effects were attenuated by SIRT1 knockdown and upregulated by mimicking SIRT1 overexpression (Ungvari et al., 2009). In addition, when the effect of resveratrol on mice was examined, it was reported that it also reduced doxorubicin-induced

cardiomyocyte apoptosis through SIRT1-mediated deacetylation (C. Zhang et al., 2011). However, microarray analysis of globa gene expression in the heart showed that most of the cardiovascular benefits of calorie restriction were achieved with a lower dose of resveratrol required to activate SIRT1 (Dolinsky & Dyck, 2011). Resveratrol; increased insulin-dependent glucose uptake in hepatocytes, adipocytes, and skeletal muscle with the induction of SIRT1 (Breen, Sanli, Giacca, & Tsiani, 2008).

Resveratrol, SIRT1 and PGC-1α work synchronously, and SIRT1 causes changes in mitochondria by causing the activation of PGC-1α (Lagouge et al., 2006). In addition, SIRT1 causes an increase in the transcription stage of these signaling pathways and an improvement in high-fat diet-induced insulin resistance (Haohao, Guijun, Juan, Wen, & Lulu, 2015). In studies, resveratrol suppresses FOXO1 by activating SIRT1 deacetylase and acts as an antidiabetic agent (Sin, Yung, & Siu, 2015). Moreover, in some experimental applications, after resveratrol treatment, mitochondrial biogenesis and oxidative phosphorylation were increased in muscle, lipid tissue, liver. As a result, it was stated that these effects are mediated by the activation of SIRT1 and its targets, PGC-1α and AMPK (Price et al., 2012).

6. CONCLUSION

In terms of cardiovascular indicators in in vitro and animal model studies, it has been reported that stimulation of SIRT1 with resveratrol in rats regulates cardiac functions (Jian, Yang, Chaudry, & Raju, 2012). In addition, resveratrol-mediated SIRT1 activation in mice also reduced plaque formation (Do et al., 2008). It has been reported that the cardioprotective effects of exercise in the aged rat heart are increased by resveratrol treatment, and this is achieved through the activation of SIRT1, which has blocking effects on FOXO3 accumulation in the nucleus (Lin et al., 2014). However, the findings obtained as a result of RNA interference experiments show that the slowing effects of resveratrol on insulin signaling pathways do not decrease with the decrease in SIRT1 expression (J. Zhang, 2006). These observations strengthen the possibility that resveratrol regulates survival independently of SIRT1 through inhibition of insulin signaling pathways (J. Zhang, 2006). However, when studies on the relationship between resveratrol and diabetes are examined, it shows that a standard has not yet been established regarding the relationship between dose and duration in resveratrol administration. In addition, resveratrol is undeniably associated with diabetes, due to its antioxidant activity, positive effects on liver glycogen, carbohydrate metabolism, and bone metabolism, by increasing insulin-dependent glucose uptake in skeletal muscle, hepatocytes, and adipocytes through stimulation of SIRT1. However, future studies are needed to reveal the effects of resveratrol on diabetes through SIRT1 activation.

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CHAPTER 7

CARE AND SPIRITUAL SOCIAL WORK ON THE AXIS OF SPIRITUALITY

Dr. Sema SAĞLIK[1], Şeyda DEMİR[2]

1 Dr. Öğrt. Gör., Sosyal Hizmet Bölümü, Esenyurt Üniversitesi
E-mail: sema.saglik@meb.gov.tr
2 Yalova Üniversitesi, Sosyal Hizmet bölümü, Sosyal Hizmet Anabilimdalı
E-mail: seydademir44@gmail.com

Vital Pulp Amputation and Techniques

The pulp is a structure found in the crown and root of the tooth and has shaped, nutritive, sensory, and protective properties. Pulp tissue is a vascularized connective tissue of ectomesenchymal origin and surrounded by a nerve network. The coronal pulp is surrounded by enamel and dentin, and the root is surrounded by dentin and cementum. These hard tissues surrounding the pulp provide mechanical support and protect the pulp against microbial rich in the oral environment. pulp tissue; It is a vascularized connective tissue of ectomesenchymal origin and surrounded by a nerve network, which has shaping, nourishing sensory and protective functions. (1)

Vasodilation and increased vessel permeability caused by inflammation in the pulp tissue cause an increase in pressure in the pulp tissue. This pressure increase activates the local feedback mechanism. According to this mechanism, increased interstitial pressure in the inflamed pulp reduces the transcapillary hydrostatic pressure difference and prevents filtration.

In addition, increased interstitial pressure helps capillaries in adjacent tissue where inflammation is not present to absorb interstitial fluid and increases lymph flow. With these two mechanisms, the fluid that causes the increase in tissue pressure is removed from the affected area, thereby reducing the tissue pressure. The fact that the pulp can protect itself for a long time after inflammation and that the inflammation regresses and pulpal health can be regained when suitable conditions are provided can be explained by these mechanisms. For the pulp tissue to be repaired, it is necessary to maintain the vitality of the pulp. For this reason, the importance of vital pulp treatments is increasing. (2-4)

Although a tooth can remain functional without being vital, it should be aimed to preserve the vitality of the pulp (5) In recent years, clinicians and scientists; emphasized the importance of maintaining the vitality of the pulp while cleaning deep caries. (6)

Our priority in pulp treatment; is to maintain the vitality of the pulp affected by caries, trauma, or other reasons. (5)

The indications, goals, and type of pulp therapy depend on whether the pulp is vital or not. A healthy pulp should be clinically asymptomatic and respond to vitality tests. (7)

amputation treatment; It is the covering of the infected or affected coronal pulp tissue with a coating agent that will help maintain the vitality of the radicular pulp, which is left behind after surgical removal and that will help maintain the vitality of the radicular pulp, which is predicted to be alive. It is one of the most applied endodontic treatments. (8-10)

The features that an ideal pulp coating agent should have can be listed as follows; (11,12)

- Should be bactericidal
- It should help the radicular pulp to heal.
- It should be biocompatible for pulp and surrounding tissues.
- It should not interfere with the physiological root resorption process.

Various materials have been tried to find an ideal capping agent in amputation treatments from past to present, unfortunately, an ideal amputation agent has not been defined among these available materials yet. (13,12)

Indications for Vital Pulp Amputation (5, 13)

- teeth where the pulp is perforated by caries or mechanical injury.
- There should be no spontaneous complaints of pain.
- There may be pain related to meals, especially sugary foods.
- Soft tissue findings (swelling, abscess, fistula) should be normal,
- There should be no radiological signs of infection.
- When bleeding is controlled with cotton pellets after a few minutes, there should be no purulent, necrosis, or excessive bleeding.

Vital Pulp amputation contraindications; (14)

- The patient has any systemic disease that will prevent treatment,
- The tooth is in a condition that cannot be restored,
- Spontaneous and ongoing pain complaints,
- Sensitivity to percussion or palpation,
- Pathological mobility,
- Presence of swelling, abscess or fistula due to infection in the pulp,
- Presence of serous or purulent drainage in the pulp,
- Pathological radiological findings:
  - ✓ Pulp calcifications,
  - ✓ Internal and external resorption,
  - ✓ Radiolucency in furcation or periapical,
  - ✓ Physiological root resorption reaches 2/3 of the root.

While performing amputation treatment, the color and duration of the bleeding in the pulp and the vitality of the pulp are important issues to be considered. Bleeding should stop within 5 minutes after the coronal pulp is removed. This indicates that the remaining root pulp is healthy. (11.14)

Targets in amputation treatment; (5)

Radicular pulp is asymptomatic, there should be no pain, fistula, and swelling in the tooth,

- Postoperatively, external resorption should not be observed radiographically.
- If there is internal resorption, it should be monitored if it is self-limiting and stable, if perforation occurs and causes bone resorption or whether there is clinical infection.

Amputation treatments are classified according to their goals (15):

Devitalizing therapy (mummification, cauterization) (formocresol, electrosurgery, laser)

- ✓ Preventive therapy (minimal devitalization, non-inducer) (glutaraldehyde, ferric sulfate, zinc oxide eugenol (ZnO))
- ✓ Regenerative therapy (inducer, reparative) (calcium hydroxide, bone morphogenic protein (BMP), mineral trioxide aggregate (MTA).

Devitalizing treatment: Devitalization was the first aim of amputation treatments for primary teeth. In the multi-session formocresol technique applied for the first time by Sweet (15), the aim is to completely embalm the tissue. They suggested that when the tissue is completely fixed, the root pulp is theoretically lifeless and sterile, so there will be no infection and internal resorption problem (15). In the following years, it was understood that the number of sessions did not affect the success of the treatment (17). (15, 17)

Preventive treatment: In this treatment, it is aimed to keep the radicular pulp completely alive, although a regeneration process has not started (Ranly 1994). Zinc oxide eugenol (ZnOE), which has been widely used since the first periods of dentistry, has also been used in amputation treatments (15) and has become the first material used in preventive treatment applications. Since ZnOE, which has a therapeutic effect when placed on healthy dentin in indirect pulp coatings, has a cytotoxic effect when placed directly on the pulp, its use as an amputation material has been abandoned (18). He suggested that glutaraldehyde and ferric sulfate materials, which are different, should also be evaluated within this group. Because glutaraldehyde is difficult to prepare and store, glutaraldehyde applications have not become widespread compared to formocresol. (15)

Regenerative treatment: In ideal amputation treatments, radicular pulp; should be vital, healthy, and completely covered by the dentin barrier formed by odontoblasts. In this case, the pulp tissue will be isolated from the damage of the restorative materials under the formed dentin barrier, thus reducing the risk of internal resorption. In addition, odontoclasts in the healthy pulp participate in the exfoliation process on time, and this process continues within physiological limits. For these to occur, repair dentin must be created by the amputation agent. (15). Over time, various pharmacotherapeutic agents and techniques have been proposed to provide treatments that meet the criteria for success. Some of these are formocresol, calcium hydroxide, ferric sulfate, glutaraldehyde, electrosurgery, laser irradiation, and growth factors. Formocresol is the most popular of these methods due to its ease of use and high clinical success (18, 19).

Partial Pulpotomy (Cvek Amputation)

It is a treatment that aims to maintain the health of the remaining coronal and radicular pulp by removing a small part of the crown pulp. (8)

When deciding on the pulpotomy treatment, the type of tooth (permanent or primary tooth), the etiology of pulp perforation (trauma or caries), root development (open or closed apex), the type of fracture (simple or complicated crown fracture), trauma-related bone and gingival injury. decide whether it is not. In primary teeth, when the pulp is perforated with caries, a total pulpotomy is preferred. On the other hand, if there is pulp exposure in permanent teeth due to trauma or caries and pulpal bleeding can be controlled within a few minutes, cvek amputation is preferred. (20-22)

After local anesthesia is applied to the tooth, it is isolated. If there is an exposure due to caries, all carious tissue in the cavity is cleaned from the periphery towards the center. Using a sterile diamond bur, the pulp tissue under the pulp exposure area is lifted by 1-3 mm to reach the healthy pulp underneath. If there is a pulpal opening due to trauma, it is removed to reach the healthy pulp of 1-3 mm in the same way. After the pulpal bleeding is controlled, the exposed pulp surface is covered with a pulp coating agent and the tooth is restored. (23)

After the Cvek amputation treatment applied by Fuks AB et al. on 63 permanent incisors whose pulp was exposed due to complicated crown fracture; It was reported that no clinical and radiological pathology findings were observed in 59 teeth, a positive response was obtained in electrical pulp tests, and dentin bridge was formed radiographically, while necrosis findings were observed in 4 teeth. With this study, it was concluded that partial pulpotomy treatment showed good clinical and radiological success. (24)

Materials and Methods Used in Vital Pulpa Amputation Treatment

Over time, various pharmacotherapeutic agents and techniques have been proposed to perform amputation treatments that meet success criteria. (18)

Formocresol Amputation

Formocresol, first introduced by Buckley in 1904 and applied by Sweet in 1930, is a strong germicide drug that provides fixation of living tissues. (18) Formaldehyde penetrates organic structures and dentin canals, fixes the bacteria present in this region, and is thought to prevent tissue destruction by binding to these proteins. (25)

After clinical studies by Buckley, a treatment protocol was developed by modifying the technique described by Sweet (19), shortening the application time of formocresol and applying it for 3-5 minutes. They reported that formocresol suppressed metabolism by playing a cytotoxic role in fixation, and following formocresol amputation in the histological sections taken, homogeneous eosinophilic tissue in the coronal 1/3 of the radicular pulp, coagulation necrosis in the middle 1/3 and vital tissue in the apical 1/3 were found. (18, 19), however, Beaver et al. stated that there are no histologically separated regions in the root pulp, and concluded that there may be different tissue responses such as fixation, internal resorption and necrosis. (18)

As a result of many studies on the toxicity and systemic spread of formocresol used in amputation treatment, this material has been accepted by many researchers as having immunogenic, mutagenic and carcinogenic effects. (11,26) For this reason, it was thought that formocresol should be diluted. It was stated that the use of 1/5 concentrations did not affect the clinical success of this material. (19.27)

Thus, despite the devastating effect of diluted cresol on vital tissues, it has been argued by researchers that the systemic spread of this material is insignificant after amputation treatment (28).

Failures of formocresol amputations are mostly detected radiologically. The first sign of unsuccessful treatment is internal resorption, usually localized at the root, close to the area where formocresol was applied. Especially in the later periods, external resorption may accompany it. With the increase in resorption, excessive mobility is observed in the tooth and a fistula usually occurs. It is rare to see pain symptoms in the failure of formocresol amputation (19).

Due to its high clinical success rate, formocresol amputation is an amputation technique that is frequently preferred in clinical practice today.

Increasing concerns about the toxicity and potential carcinogenicity of formocresol have led researchers to alternative methods to find an ideal pulp coating agent. (29)

Clinical Application

The tooth is isolated using local anesthesia. The access cavity is opened by following the endodontic rules. The coronal pulp chamber is removed with a sharp and sterile instrument. Bleeding is controlled with cotton pellets for 3-4 minutes. If bleeding continues, root canal treatment is started. Cotton pellets impregnated with formocresol are kept in the canal mouths for 3 minutes. After the drug is removed, the pulp should be non-bleeding and have a brown appearance. Following these procedures, zinc oxide eugenol cement is placed in the pulp chamber and restored with PÇK (stainless steel crown) or other restoration materials. (18)

Calcium Hydroxide Amputation

In an ideal amputation treatment, it is expected that the remaining pulp is healthy and vital, and it is covered with an odontoblast-limited dentin layer. In this case, it becomes important to use an amputation agent that will stimulate the formation of reparative dentin. (18). Calcium hydroxide was the first material used in the treatment of amputation, which was shown to have the capacity to induce dentin regeneration (15).

Today, Ca(OH)2 is widely used as a capping agent because it is the most classical agent that can stimulate dentin regeneration and keep the root pulp alive. Ca(OH)2 has a high pH value and has a bactericidal effect. It can neutralize bacterial acids and lipopolysaccharides in dentin. Thus, it causes the release of growth factors attached to dentin. (30)

Due to the high pH of the hydroxyl ions in the calcium hydroxide content, it causes a chemical injury to the pulp. Following this injury, superficial coagulation necrosis and moderate inflammation occur. This is the superficial, germ-free, slow death of pulp tissue. The proteolytic ferments in the necrosis layer are eliminated and there is also a coagulation in the pulp. This necrosis layer formed; induces differentiation of adjacent healthy pulp tissue, fibroblasts, or undifferentiated mesenchymal cells into odontoblasts. This event is especially seen during the healing events observed in vital pulp treatments such as vital amputation and direct capping. (31.32)

In the repair process, after the inflammatory response, the area of necrosis is filled with dystrophic calcifications and the repair dentin, namely the dentin bridge, is formed (Carrotte 2005, Briso et al 2006, de Souza Costa et al 2008). The resulting calcified tissue is called osteopontin. The alkaline pH of calcium hydroxide not only neutralizes the lactic acid

released from osteoclasts but also prevents the dissolution of the mineral components in dentin. At the same time, it plays an important role in the formation of hard tissue by activating alkaline phosphatase (32-34). The stimulation created by calcium hydroxide is in a delicate balance between repair and resorption (15). However, when the balance is disrupted destructively, the process fails the treatment. (18)

Particular attention should be paid to pulpal bleeding after pulp amputation, especially in calcium hydroxide amputations (35). In the clinical and radiological evaluations of calcium hydroxide amputations, a success rate of 57-80% has been reported (36,37). In clinical studies comparing calcium hydroxide and formocresol, it has been reported that calcium hydroxide is not as successful as formocresol (35). Internal resorption is the main cause of failure of calcium hydroxide amputations. Therefore, it has been reported that calcium hydroxide is not a strong alternative to formocresol as a material that is not preferred much with low clinical and radiological success in primary tooth amputations. (18,36) There is no strong consensus regarding the use of this material due to failures due to failure to prevent internal resorption. (15)

Ferric Sulfate Amputation

20% ferric sulfate (Fe2(SO4)3) (Monsel solution), a strong hemostatic and non-aldehyde group compound was first used in France in 1857. In dentistry, it is generally used to stop bleeding in surgical operations and for gingival retraction. Although it is not fixative, it has only bacteriostatic properties. To control bleeding, gentle application of a 15.5% solution of ferric sulfate is recommended, intermittently for about 15 seconds. The short application time provides clinicians with great convenience when treating children. (38) Due to the low pH of the solution due to its direct application to the pulp, iron and sulfate ions appear. Although it has been reported that these ions cause the precipitation of blood proteins as a result of the interaction of iron and sulfate ions with the blood, causing mechanical blocking of the cut vessels, the actual mechanism of action is still debated.

The metal-protein complex formed in the pulp tissue acts as a non-toxic barrier against irritants. (39) Since ferric sulfate provides hemostasis by precipitating blood proteins without forming blood clots, it is thought that failures such as chronic inflammation and internal resorption can be prevented by eliminating failures that may occur due to extravascular clot formation. (40) However, internal resorption and radiolucency areas in furcation were also observed in ferric sulfate amputation. (39)

In previous studies, the presence of a clot formed between the pulp tissue and calcium hydroxide was mentioned as the cause of calcium hydroxide

failure. For this reason, the necessity of improving bleeding control was considered and the use of ferric sulfate together with calcium hydroxide was investigated. In later periods, ferric sulfate began to be used alone in the treatment. In clinical studies, success rates similar to formocresol were seen for ferric sulfate in amputation treatments in primary teeth. (39,41).

Clinical Procedure

The tooth is isolated by performing local anesthesia. The pulp chamber is opened by adhering to traditional endodontic rules. The coronal pulp is removed with a sharp and sterile instrument. Bleeding is controlled within 3-4 minutes with cotton pellets. If the bleeding cannot be controlled, the next treatment step, root canal treatment, is planned. In the canal mouths, 15.5% ferric sulfate is contacted with the pulp tissue for 10-15 seconds. If bleeding control is not achieved in the first application, it can be applied a second time. After this stage, it is thoroughly washed with physiological saline. The cavity is thoroughly dried with cotton pellets and the tooth is restored by placing zinc oxide eugenol. (18)

Glutaraldehyde Amputation

Glutaraldehyde, due to its strong antimicrobial and low toxicity properties, is used in deciduous tooth pulpotomy treatments and establishes tight bonds with amino acids of proteins, and provides a more stable and irreversible fixation than formocresol.

Since it has a larger molecular size than formocresol, it diffuses more slowly into tissues. In addition, it can stabilize proteins faster, irreversibly, and completely. In addition, since its spread is limited to hard tissues, it does not cause periodontal irritation. Although it is less toxic and a better fixative, this material is not widely used because it is not as clinically successful as formocresol. Due to the instability of glutaraldehyde in its pure form, the preparation of buffer solutions is considered among its disadvantages. (18,38,42)

Clinical Procedure

The tooth is isolated by performing local anesthesia. The pulp chamber is opened by adhering to traditional endodontic rules. The coronal pulp is removed with a sharp and sterile instrument. Bleeding is controlled within 3-4 minutes with cotton pellets. If the bleeding cannot be controlled, the next treatment step, root canal treatment, is planned. Cotton impregnated with 2% glutaraldehyde is kept in the duct mouths for 5 minutes. After the drug is removed, the pulp should be non-bleeding and have a brown appearance. Zinc oxide eugenol is placed and the tooth is restored. (18)

Mineral Trioxide Aggregate (MTA) Amputation

In recent years, the use of MTA as a preferred material for pulp treatments has come to the fore. It was described by Torabinejad et al. It was approved for use in humans by the FDA in 1998. Clinical studies have shown that MTA has similar or better success than formocresol and ferric sulfate. (13, 43-45)

Its chemical components are related to Portland cement, and it is formed by mixing dicalcium silicate, tricalcium silicate, tricalcium aluminate, tetra calcium aluminum afferent, and gypsum, and bismuth oxide is added to increase its radiopacity. (38)

While it was originally developed as a retrograde filler in periapical surgical treatments, today it has many uses, including in the treatment of perforations, vital pulp treatments, and apexification. (46.47)

MTA applied to pulp tissue; It causes proliferation, migration, and differentiation of cells responsible for collagen matrix production to this region. With the mineralization of the formed matrix, first osteopontin and then tertiary dentin are formed. (48-50) Ainechchi et al. When they compared pulpotomy treatments made with calcium hydroxide and MTA, it was reported that although the hard tissue formed with calcium hydroxide contains deficiencies and tunnel defects such that bacterial leakage may occur, this situation was not observed in the dentin bridge formed with MTA. (51) Histologically, according to Ca(OH)2 of MTA; It was observed that a thicker dentin bridge formed, less pulpal inflammation, hyperemia, and pulpal necrosis. (52)

Difficult to manipulate the material, long curing time, causing discoloration on the crown, and high cost was seen as disadvantages, and researchers started to search for new materials. (53)

Clinical Procedure

The tooth is isolated by performing local anesthesia. The pulp chamber is opened by adhering to traditional endodontic rules. The coronal pulp is removed with a sharp and sterile instrument. Bleeding is controlled within 3-4 minutes with cotton pellets. If the bleeding cannot be controlled, the next treatment step, root canal treatment, is planned. Following the company's recommendations, powder and liquid are mixed and placed in the channel mouths in 3-4 mm thickness. It is condensed with the help of a damp cotton pellet. Zinc oxide eugenol is placed in the pulp chamber and the tooth is restored or preferably 1 day later. (18)

Electrosurgical Amputation

The systemic spread and toxic effects of some agents used in primary tooth pulpotomy suggested that bleeding control should be performed

with non-pharmacological approaches such as electrosurgery and laser during direct pulp treatments. (54) When the success of pulpotomy applied with formocresol and electrosurgery methods were compared; Some investigators reported that there was no difference between the clinical and radiographic success of formocresol and electrosurgical pulpotomy. (55.56) Öztaş et al. formocresol pulpotomy are histopathologically superior to the electrosurgery method (57); El Meligy et al. reported that less histopathological reaction occurred in pulpotomy treatment with electrosurgery. Although the study of this procedure is limited, encouraging results have been reported. (58)

Clinical Procedure

The tooth is isolated by performing local anesthesia. The pulp chamber is opened by adhering to traditional endodontic rules. The coronal pulp is removed with a sharp and sterile instrument. Bleeding is controlled within 3-4 minutes with cotton pellets. If the bleeding cannot be controlled, the next treatment step, root canal treatment, is planned. A U-shaped electrode to the pulp tissue at the canal orifices is coagulated with a high-frequency current of the pulp at the canal orifices with brush-like strokes. After the application, the pulp should be non-bleeding and have a brown appearance. Zinc oxide eugenol is placed and the tooth is restored. (18)

Laser Amputation

After long studies, FDA allowed the use of laser technology in 1997, cleaning and preparation of carious cavities, aesthetic dental treatments, periodontal surgery, periimplantitis treatment, treatment of aphthae and herpes, reduction of dentin hypersensitivity, evaluation of pulp vitality, direct pulp coating, pulpotomy, and root canal disinfection. It has many uses such as Laser technology has a wide variety of applications in pediatric dentistry. (18, 38, 59, 60)

Laser irradiation creates a limited area of coagulation in the pulp tissue it contacts. However, the underlying tissue is in good condition and is protected from the negative effects of the pulp base material. (18)

When the success of direct pulp coating with Ca(OH)2 after carbon dioxide laser application is compared with direct pulp coating performed with only Ca(OH)2, the clinical success in the laser applied group was 93% after 2 years of follow-up; In the control group, the success rate was 68%. (61)

Jayawardena et al. stated that coating the pulp with calcium hydroxide after the use of Er: YAG laser did not cause any pathological response and provided dentin bridge formation. (62)

However, in some studies, carbonization, necrosis, and inflammation of the pulp were observed after pulpal amputations with laser, while the repair was minimal. (38) In a review, it was seen that there is weak evidence that laser amputation applications can improve the results of treatment. He concluded that further studies are needed. (63)

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CHAPTER 8

MATERNAL ATTACHMENT AND INFERTILITY

Tuğba TAHTA[1], Yeliz KAYA[2]

1 1Ankara Medipol Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu, Ameliyathane Hizmetleri Programı. Ankara, Türkiye orcid.org/0000-0003-0190-977X
2 Eskişehir Osmangazi Üniversitesi Sağlık Bilimleri Fakültesi, Doğum ve Kadın Hastalıkları Hemşireliği ABD, Eskişehir, Türkiye orcid.org/0000-0003-4277-3960

1. INTRODUCTION

Maternal attachment is a process that begins during pregnancy, motivates to gain satisfaction with the role of mother, and further strengthens the emotional component of maternal identity. Infertility is a public health problem, and more than 10% of the world's population has difficulty conceiving naturally. According to the maternal attachment theory, a pregnant woman's emotional attachment to her baby is formed during pregnancy and gradually increases. As the gestational week increases and pregnancy progresses, maternal attachment also increases in direct proportion. In vitro fertilization (IVF) offers a way to solve the problem of infertility. When a woman becomes pregnant through IVF and goes through a different conception process, these extraordinary experiences can affect the development of maternal attachment.

With his article, we aimed to explain the relationship between infertility and maternal attachmentin the light of the articles reviewed by using the keywords 'infertility', 'maternal attachment', 'maternal role', and medical search engines.

2. ATTACHMENT THEORY

Attachment theory is the tendency of the individual to expect closeness from another person and to feel safe when this person is with him. The founders of this theory are John Bowlby and Mary Ainsworth. Attachment theory or concept emerged as a child development paradigm in the 1950s thanks to the work of John Bowlby and Mary Ainsworth. attachmentis a term used to express the positive bond between a child and a parent or caregiver. It explains how the early relationship which develops between an infant and their primary caregiver shapes the infant's development and lays the foundation for later relationships in life.

Children readily seek out guides who ensure both physical and emotional survival and facilitate exploration and discovery. In safe attachments, parents or caregivers may regulate the child's emotional experiences by meeting their needs of safety. In insecure attachments, the child's safety may be implicitly or explicitly threatened.

3. MATERNAL ATTACHMENT

Transition to motherhood is an essential developmental life event. Becoming a mother is an important developmental event in a woman's life. In fact, being a mother involves the transition to a new reality that exists for women but is unknown. This transition may require restructuring of behaviors, responsibilities and goals in order to achieve a new concept of role and identity.

The transition to motherhood can be facilitated or hindered by women's conditions, cultural beliefs, attitudes, socioeconomic status, preparation for pregnancy, and knowledge. Creating a mother identity in the process of becoming a mother contributes to the psychosocial development of women. The mother-infant relationship in the early period is critical. It lays the foundation for the child's future social, emotional, and cognitive development. Maternal behaviors such as sensitivity, acceptance, and cooperation are associated with establishing and maintaining a positive relationship with her baby. Maternal attachmentis a process that begins during pregnancy, motivates to gain satisfaction with the role of mother, and further strengthens the emotional component of maternal identity. The main theories about motherhood are Mercer's Theory of Being a Mother and Rubin's Theory of Maternal Role Acquisition.

3.1. Maternal Role Acquisition Theory

It is one of the main theories about motherhood and Rubin's maternal role acquisition theory. Rubin describes maternal role acquisition as a process that leads a woman to reach her maternal role identity. Rubin defines the later stages of the process that begins in pregnancy as role-playing, imitation, introjection-reflection-rejection, fantasy and identity. The woman moves from imitating observations and seeking information to seeking expert models, role-playing, and imagining herself as a mother. The woman introjects the observed behaviors of others, accepts the behaviors that are suitable for her and rejects the behaviors that she thinks are not suitable for her. Rubin suggested that four maternal duties must be fulfilled for a woman to have a mother identity.

These tasks are;

1. Providing safe passage for herself and her child,
2. Ensuring the child's acceptance by people,
3. Attaching to the unborn child
4. Learning to give from herself.

Maternal role acquisition creates a secure attachmentto the baby and increases the woman's and child's confidence to support their cognitive, behavioral, and physical development. Taking care of the baby and spending time without the help of others provides the development of a sense of pleasure and satisfaction for the role of mother in women.

3.2. Theory of Being a Mother

Mercer, a student of Rubin, started developing the theory of gaining the role of mother in the 1960s. Mercer stated that gaining the maternal role is a process the mother gets her role qualities and adds behaviors to the role group.

Mercer has defined acquiring the role of the mother as a process that includes four stages.

1. The waiting phase: preparation for the birth of a child during pregnancy;

2. Formal stage (role playing): increased attachment, familiarity and learning how to care for the baby;

3. Informal stage (role acquisition): Increased self-confidence in response to the infant's privileged characteristics, establishing self-mothering behaviors, and caring for the newborn;

4. Personal stage (mother role identity): The joyous relationship between mother and newborn, love of sucking, and feeling empowered.

While the woman passes through these four stages, she moves from imitating the mothering behaviors of role models and learning the expectations of the role, to following the rules and instructions of others, and finally to developing her own mothering behaviors, gaining self-confidence and competence. According to Mercer, becoming a mother is a constantly changing and evolving process. Therefore, Mercer suggested replacing the term "maternal role acquisition" with "motherhood". Because she thought that the theory of gaining the maternal role did not adequately explain how motherhood changes as the mother herself and her children grow and mature.

She renamed the stages of being a mother in parallel with the stages of the mothering role's ability;

1. Commitment, attachment, and preparation (throughout pregnancy)

2. Meeting, application, and physical recovery (first 2 weeks postpartum)

3. Approaching normalization (2 weeks to 4 months postpartum)

4. Acquiring maternal identity (4 months to 1 year postpartum)

According to Mercer, maternal role satisfaction refers to a kind of satisfaction, pleasure, and pleasure that a woman experiences while interacting with her baby and performing maternal role duties after the baby's birth.

Rubin and Mercer described the role-gaining process of mothers, from the onset of pregnancy to the four-month postpartum period, as a mental experience. Achieving a safe pregnancy for the mother and the baby, ensuring the acceptance of the baby, attachmentof the pregnant woman to her baby, the role of the father, the diseases of the mother, and the self-confidence were evaluated. There is evidence to suggest that Maternal attachmentand love have their origins in pregnancy. The development of maternal-fetal attachmentduring pregnancy is a precursor to mother-

infant attachmentthat occurs after birth and plays a crucial role in the child's future cognitive development and physical health. Maternal-fetal attachmentgradually increases in the second and third trimesters.

4. INFERTILITY AND MATERNAL ATTACHMENT

4.1. Infertility

Infertility is defined as the inability to conceive despite unprotected sexual intercourse for 12 months or longer. It is also known as a clinical disease of the reproductive system. Infertility is a common public health problem. More than 10% of the world's population has difficulty conceiving spontaneously. Infertile couples face difficulties in physiological, psychological and social terms. The diagnosis and treatment process of this disease affects infertile couples in many ways. These effects are generally negative. The stress of infertility builds up over time as couples actively seek treatment for their illness. Uncertainty about the success or failure of infertility treatment also increases anxiety. Many women face mental problems at the beginning of infertility treatment. In particular, women who have had IVF from assisted reproductive techniques often become sad, thoughtful, depressed and anxious due to the uncertainty, complexity and often low success rate of treatment methods. This may threaten the results of treatment and prolong the duration of treatment. Even if conception occurs after treatment, long-term anxiety causes a decrease in uteroplacental blood flow, changes in uterine oxygenation, abnormal fetal heart rate, and an increased probability of preterm birth with stimulation of the autonomic nervous system. In high-risk pregnancies with a history of infertility, some hormones (such as cortisol, catecholamine, beta-endorphin, epinephrine) secreted in response to fear and anxiety prevent and impair the functioning of uterine smooth muscles, adversely affect the contractile capacity of uterine smooth muscles and cause deterioration in cervical dilatation. This prolongs labor and increases pain. So it will cause anxiety. Women who become pregnant after infertility treatment are at risk for multiple pregnancies, pregnancy complications, preterm labor and other birth-related problems.

4.2. Physical Factors Affecting Maternal attachmentin Infertile Woman

The physical signs and symptoms experienced by the pregnant woman during pregnancy include the presence of signs and symptoms observed during pregnancy. Studies and evidence regarding the effect of physiological symptoms of pregnancy on maternal attachment are limited. Studies have mostly focused on women who spontaneously become pregnant. Infertile women who became pregnant by in vitro fertilization after infertility treatment may interpret the normal physical symptoms

experienced during pregnancy more negatively than women who became pregnant spontaneously and think that these indicate a problem with the pregnancy. If these signs and symptoms are interpreted as a sign that something went wrong during pregnancy, it can negatively affect maternal attachment. Women who have had IVF often experience physical symptoms during pregnancy that could affect maternal attachment. Many women undergoing IVF treatment from assisted reproductive techniques use gonadotropin therapy to stimulate ovulation. The most important complication of this treatment is umbilical hyper-stimulation syndrome (OHSS). This syndrome causes many physical symptoms. Mild OHSS symptoms include abdominal pain, acid buildup, and bloating. Severe OHSS symptoms include nausea, vomiting, fluid-electrolyte imbalance, shortness of breath, and diarrhea due to fluid accumulation in the abdominal cavity and chest. The development of OHSS and the presence of symptoms may be a condition that may prevent maternal attachment.

4.3. Psychological Factors Affecting Maternal Nonding in Infertile Women

Maternal-fetal attachmentdevelops as a desire to protect the unborn child as the pregnant woman begins to perceive and interact with the fetus, developing an emotional bond with the developing fetus. According to the maternal-fetal attachmenttheory, a pregnant woman's emotional attachmentto her unborn child gradually increases during pregnancy, and varying degrees of attachmentdevelops as pregnancy progresses. IVF offers a way to solve the problem of infertility. When a woman becomes pregnant through IVF and goes through a different conception process, these extraordinary experiences can affect the development of maternal attachment.

Even if an infertile couple has a healthy baby, they may continue to struggle with the psychological aspects of infertility. Although most of the studies focus on the response of the infertile individual, some studies have found that specific factors affect only the infertile individual, not the spouse. Women's internalization of social norms regarding gender roles causes them to experience intense depression, stress, and low self-esteem. This has led to more infertility problems, self-blame, and distress. Pregnancies that occur after multidimensional problems caused by infertility cause a paradoxical life that causes physiological, psychological, and sociological changes. Pregnant women with a history of infertility are prone to mental problems due to anxiety, depression, and feelings of guilt. Therefore, women who become pregnant after infertility treatment can often reflect their negative feelings on their pregnancy. Covington and Burns (26) claimed that the transition from having a 'vicious identity' to a 'mother identity' is particularly psychologically challenging and this change does

not take place fully until the baby is born. Even if pregnancy occurs after a difficult treatment process, infertile women face many psychological and physical problems until their babies are born. In a study, it was reported that even after a successful pregnancy, some women who received infertility treatment are negatively affected by the process and have high stress.

In a study investigating the effects of infertility on maternal-fetal attachment, coping styles, and self-concept during pregnancy, it is reported that the infertile women perceived transition to parenthood differently, experience higher levels of anxiety and are negatively affected by maternal-fetal attachment. In a study examining the parental status after infertility treatment, it was reported that the psychological aspects of infertility may remain, and the presence of complications in the baby (high-risk conditions such as low birth weight, long-term developmental or behavioral problems) may affect mother-infant attachment. Women who give birth after getting pregnant with assisted reproductive techniques (ART) experience mild to moderate mental disorders compared to those who conceive spontaneously. However, in a study examining the characteristics and attitudes of the parents of children born using ART, it was reported that there was no difference in the psychosocial development or Maternal attachmentof the parents. In a study comparing pregnancies after ART with natural pregnancies; women have more positive attitudes towards the pregnancy and stronger mother-infant attachmentafter IVF treatment. In a study conducted with Taiwanese women who became pregnant with ART, mother-infant attachmentstarted during pregnancy and ART did not affect attachment. In another study, Australian women who became pregnant with ART reported better mental health during pregnancy in terms of mood disturbance, quality of the relationship with their close partner, and emotional attachmentto the baby compared to women who became pregnant spontaneously. In another comparative study, the rates of mother-infant attachmentafter IVF were the same as those of other mothers, and the mode of conception did not affect prenatal attachment. In a study examining perinatal attachmentin pregnant women who became pregnant naturally and were treated with infertility, it was reported that women who became pregnant after infertility treatment had higher mother-fetus and mother-baby attachment scores.

5. CONCLUSION AND RECOMMENDATIONS

Many role gains take place in newborn mothers. These roles are; It includes change of life and change of professional identity, change of personal freedom, change of autonomy. Indecision is normal in women who have just given birth, as these role changes affect social life and leisure activities. The persistence of this sense of indecision and uncertainty may hinder the development of maternal identity during pregnancy and may have a negative impact on early maternal behaviors.

A woman who conceives with ART under much more difficult conditions may have different thoughts about motherhood. It is possible for women who conceive with ART to feel doubt, anxiety, uncertainty, fear or mixed feelings. Therefore, it is possible for women who conceive with ART to receive less social support than those who conceive spontaneously. Providing social support to women who used the ART method during pregnancy will contribute positively to maternal-fetal attachment. Social support is a critical factor for prenatal psychosocial adjustment. It helps the health and role adaptation of expectant mothers and that pregnant women with social support experience significantly less stress. The more social support women receive, the better their adaptation to pregnancy. Social support from family members and peers can also contribute significantly to Maternal attachmentdevelopment.

Insufficient knowledge about pregnancy could increase anxiety, so increasing the knowledge positively affects the outcome. Therefore, one of the most important responsibilities of health personnel is to reduce the anxiety of women during treatment and pregnancy, so that treatment measures achieve more desirable results. For women who become pregnant through ART, prenatal information and maternal identity development training could be beneficial for them to adapt to postnatal conditions, respond positively to the baby's behaviors, and develop maternal-fetal attachment. Psychological support groups should be established in ART clinics. In these groups, both mother and father candidates should be allowed to express their feelings and beliefs, and share their expectations and concerns.

It is known that relaxation training is effective in increasing anxiety and maternal-fetal attachmentin women who become pregnant with the IVF method. Although there are other methods to reduce anxiety, relaxation techniques could be used to relax women due to their ease of use.

Attachment during pregnancy can give the mother more self-confidence, making it easier to adapt to new roles and conditions that change after birth. Postpartum attachment allows the mother to respond positively to her baby and her behavior. For this reason, the greatest responsibility of health personnel is to reduce anxiety during pregnancy and postpartum, provide social support, help solve their psychological problems with support groups, and help them relax. Thus, treatment measures will lead to more desirable results. Support groups for women who conceive through IVF could be formed in a way to reduce the stresses associated with the procedure and promote maternal identity and the role of motherhood.

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CHAPTER 9

PEEK APPLICATIONS IN ORAL AND MAXILLOFACIAL SURGERY

Assistant Professor- Damla TORUL[1]

1 Ordu University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery E-mail:damlatorul@gmail.com

1. Introduction

Biomedical implants aim to restore the function and esthetic of damaged tissues to provide normal activity again. However, because of the complicated nature of the human body an optimum material that can meet all functional and esthetic demands is challenging.[1,2] As for the modern biomaterials implanted human body, they meet some essential properties such as biocompatibility, bio functionality, aesthetics and similar characteristics with surrounding tissues. Various biomaterials have been designed to provide a match between the implant and the neighboring tissues to achieve successful outcomes.[1,3-5]

The most widely used biomaterials in medicine are precious metals like gold, cobalt chrome alloys, stainless steels, and mercury-based alloys.[5] However, these metals have shortcomings like corrosion and poor handling. In 1967 use of titanium was introduced in the field of maxillofacial surgery.[6] Titanium has desirable mechanical properties, biocompatibility and can overcome the pitfalls of the other metals previously used. Thus, titanium has become the gold standard to use in the maxillofacial area.[6-8] However, titanium also has disadvantages such as limited fatigue life, allergic potential, high modulus of elasticity which leads to stress shielding and bone resorption, generation of wear debris, releasing of harmful metal ions, and radiodensity.[1,2,6,9-11]

Despite the advances in the biomedical area and significant improvements in biomaterial research, an optimum material is still an area of interest. Nowadays, because of the problems like corrosion and harmful ion release, demand for metal-free materials is increasing.[4] Also, to have similar properties with surrounding tissues is another demand for the new materials. In this point of view development of "isoelastic" materials those stiffnesses comparable with bone has considerable attention.[1,12] Poly-ether-ether-ketone (PEEK) is a thermoplastic high-performance polymer considered to be replaced metallic materials. PEEK has been offered commercially as implant material since 1998. Due to its elastic modulus matching the cortical bone, PEEK is considered as a plausible alternative to traditional implant materials such as titanium in the field of traumatology, orthopedics, and maxillofacial surgery.[13,14]

2. PEEK

2.1. The history of PEEK

Polyaryletherketones (PAEKs) have been developed by English scientists in 1978 and subsequently has been used in various areas such as cable insulation, aircraft manufacturing, bearings, piston parts, turbine blades, and compressor plate valves etc., commercially in the 1980s. Af-

ter the biocompatibility was confirmed by the 1990s, applications of the PAEKs were introduced as an alternative to metallic biomaterials in many areas of medicine. PEEK is a preceding member of the PAEKs polymer family.[12,15] The U.S. Food and Drug Administration certified PEEK as an implant biomaterial in the 1990s.[16]

2.2. Structure and Properties of the PEEK

Chemical Structure

PEEK is a thermoplastic high-performance polymer, which is the dominant member of the PAEK family composed of an aromatic backbone chain, interconnected by ketone and ether functional groups (Figure 1). The aromatic rings make PEEK unaffected to thermal, mechanical forces, oxidative attacks, and high temperature. Thus, it has remarkable physical properties, biocompatibility, and stability. With the basic chemical formula (-C6H4-O-C6H4-C6H4) amorphous PEEK is formed in three grades of viscosity.[14,17] All these properties make PEEK an alternative material that can be used in medicine and dentistry.[18]

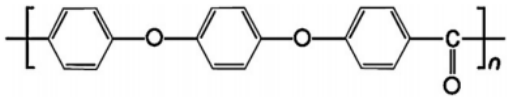

Figure 1.3 Chemical structure of PEEK.

Figure 1. *Chemical structure of the PEEK*[12]

Physical Properties

PEEK is a semicrystalline linear polycyclic aromatic polymer with high- thermal stability (exceeding 300 ◦C), mechanical and chemical resistance.[19] PEEK is a classically two-phase semi-crystalline polymer, and the two-phase morphology is made up of crystalline regions dispersed in amorphous regions. PEEK has high stability, insolubility, low density. PEEK is white, radiolucent, and rigid material which does not cause allergic reactions and show low affinity to plaque. PEEK is chemically and physically stable either during the sterilization process,.[3,12,18,19] PEEK has excellent biocompatibility and has no genotoxic or mutagenic effects.[15,20] In the film structures produced from this polymer, the thinner the film, the more transparent and ss the thickness increases, the color becomes dull and amber color becomes noticeable.[21] PEEK is compatible with the imaging modalities.[22]

Mechanical Properties

Flexural modulus, density, thermal conductivity, and young's (elastic) modulus of PEEK is shown in Table 1. Properties like elasticity modulus

and tensile strength are close to that of bone, dentin and enamel structures of human. It is also can be implemented with several reinforcing materials and resistant to wear.[18,19,21]

Table 1. *General properties of PEEK*[21,23]

Density (Kg/m3)	1300
Elastic Modulus (GPa)	3-4
Yield stress (MPa)	107
Tensile strength (MPa)	80
Poisson's ratio	0.38
Glass Transition temperature (K)	416
Resistivity (ohm.cm)	5.1016
Melt transition temperature (K)	616
Thermal conductivity (W/Mk)	0.29
Flexural modulus (MPa)	140-170

2.3. PEEK versus Titanium

Because of sufficient mechanical properties and biocompatibility titanium and its alloys are considered as the first choice.[2,24,25] However, some disadvantages of titanium can be listed as:

- Local allergic reactions and immunological responses related to the release of metal ions[2,16,26]
- Corrosion[16]
- Not transmitting the light titanium can lead to esthetic concerns[16,25,26]
- The mismatching in elasticity modulus of titanium and bone may cause "stress-shielding"[10,24]
- High affinity to plaque deposition is an important pitfall of titanium which may cause peri-implantitis[16]
- Hypersensitivity to titanium it has been reported in up to 0.6 % of cases.[24]
- Generally not compatible with imaging modlites[24]
- Surface deterioration related to peri-implantitis[2]
- The increasing demand for metal-free biomaterials[25]

force researchers to explore alternative biomaterials that overcome the shortcomings of the titanium. In the late 1990s, PEEK was introduced as

an alternative in medical areas, including orthopedics, maxillofacial and spine surgery.[13,14,18] It has been suggested that PEEK has some advantages that can overcome the shortcomings of titanium.[2,19,20,27]

✓ The close an elasticity modulus of PEEK can reduce the stress shielding

✓ PEEK is associated with hypersensitivity or allergic reactions rarely

✓ No genotoxic or mutagenic effects

✓ Radiolucent and compatible with imaging modalities

✓ Because of its color more aesthetic

✓ Because of the versatile nature PEEK can be prepared for a specific purpose

2.4. Improvement of the PEEK Bioactivity

PEEK has gained an increasing attention because of its mechanical, chemical properties, and radiolucent appearance, and excellent biocompatibility. However, the bio inert and hydrophobic nature of the pure PEEK result in the low osteointegration between the PEEK implants and the surrounding structures.[1,28] Despite these excellent mechanical and chemical properties, its bio inertness pose a big barrier for osseointegration.[2,15,24] Thus, the PEEK needs to be improved in terms of increasing this capacity. Surface modification and production of PEEK composites are the two main ways to improve the capacity of the PEEK material.[15,29] There are several experimental studies that have been tested the osseointegration of PEEK implants with various modifications, on dogs, rats, sheep, rabbits, and pigs.[24]

Surface modification

Surface modification can be performed either with a chemical treatment such as wet chemistry modification and sulfonation treatment, and physical treatments like plasma modifications. Regarding surface coating, several materials have been used like titanium dioxide, titanium, diamond-like carbon, gold, and hydroxyapatite (HA).[15,30,31]

Composite Preparation

Creating a composite material by implementing PEEK with a bioactive material is considered as another reliable way to increase the bioactivity of PEEK. PEEK composites are classified depending on the size as conventional PEEK and nanosized (<100nm), (Figure 2).[10,15,32]

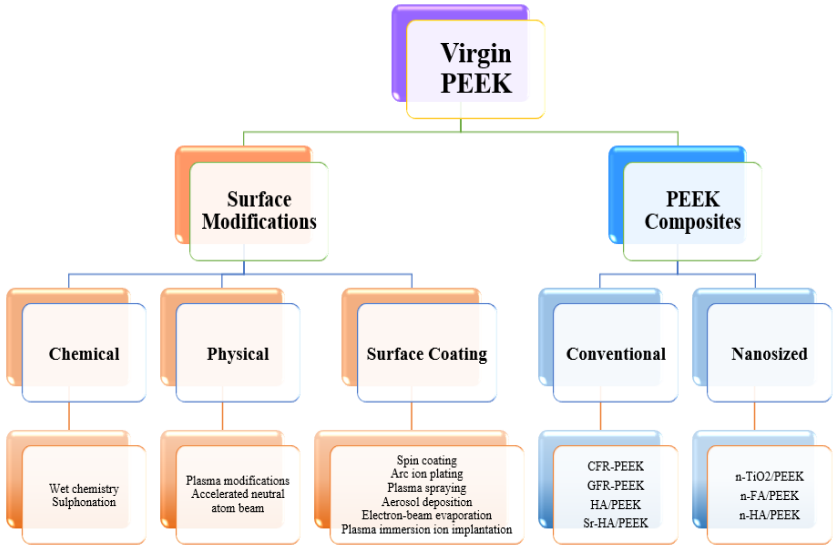

Figure 2: *Improvement of the bioactivity of PEEK*[31]

2.5. CFR-PEEK

The carbon reinforced PEEK (CFR-PEEK) was the first composite of PEEK used for biomedical applications, have more attention recently.[11] CFR-PEEK is a composite material including carbon fiber sheets, in varying directions, embedded within PEEK.[9]The polymer can be manufactured by extrusion, injection molding, or machining. The mechanical properties of CFR-PEEK are determined by the carbon fibers. Short fibers less than 0.4 mm that aligned randomly inside are called short CFR-PEEK. If the carbon fibers run through the width, then it is named as long CFR-PEEK. Being bigger than 2000 MPa the tensile strength of the l long CFR-PEEK is, higher than short the CFR-PEEK which has 170 MPa tensile strength. With the increase of the carbon fibers ratio, the tensile strength and the elasticity modulus increase.[9,10,23] PEEK reinforced with 30% carbon fibers has an elasticity modulus close to that recorded on the cortical bone.[33]

For medical uses, the modulus of elasticity of materials must be close to that of human bone.[23,34] To overcome the stress shielding and bone resorption, PEEK can also be manufactured with an elasticity modulus that matches the modulus of both cortical and cancellous bones.[11,35] The modulus of elasticity of CFR-PEEK closer to the bone compared with titanium alloy, since the modulus of elasticity 12 to 20 GPa for cortical bone, and 1 GPa for cancellous bone.[9]To date CFR-PEEK has been used in spinal surgery as cages, traumatology as fixation material, cardiac, neurological and orthopedic implants, and maxillary obturator prostheses.

Because of the high fatigue strength and toughness of CFR-PEEK it can reduce the implant fracture.[15,35] The radiolucency and compatibility of imaging modalities of CFR-PEEK are remarkable characteristics that allow the monitor fracture reduction and healing.[9]

2.6. PEEK Usage Areas in Maxillofacial Surgery

2.6.1. Dental Implants

Dental implants have become a reliable treatment option for the rehabilitation of the tooth loss since the introduction of the osteointegration phenomenon by Branemark and colleagues at the end of the 1960s. Nowadays implant therapy is increasingly used with higher success rates and reported to increase the quality of daily life of the patients. Because of sufficient mechanical properties and biocompatibility titanium and its alloys are considered as the first choice in the field of oral implantology.[2,24,25] However, because of some disadvantages of titanium and other ceramic alternatives, they are not considered as ideal option for an optimum dental implant. Thus, modified PEEK materials have been recently popular as a plausible option for oral implant applications.[16] Results of in vitro and in vivo studies which were conducted with different surface modification methods already noteworthy.[11,24,26,36]

In vitro and FEA findings

The research about the PEEK in dental implant applications are generally conducted in vitro, in vivo, and finite element analysis (FEA) studies with various evidence.

FEA Studies

Tretto et al.[37] explore the stress in dental implants with alternative materials including PEEK with FEA. They found increased stress in bone around the implant due to the implants with materials having lower elastic modulus like PEEK. In a similar study conducted by Bataineh et al.[38] stress distribution in peri-implant bone was evaluated in the usage of CRF-PEEK by means of FEA. They suggested that the replacement of titanium with PEEK implant does not show any advantages. In terms of the patients with bruxism Mourja et al's[39] FEA study found that CFR-PEEK and titanium implants exhibit similar stress on the bone under loading. Another study comparing the biomechanics of CFR-PEEK, pure PEEK, zirconia, glass fiber-reinforced PEEK (GFR-PEEK) and titanium implants using FEA reported that CFR-PEEK implants showed balanced biomechanical behavior.[40]

Similarly in the Hassan et al.'s[41] study biomechanical behavior of titanium, CFR-PEEK, ceramic-filled PEEK and pure PEEK models

compared and suggest that titanium is the most successful material. Sarot et al.[42] explore the stress distribution of titanium and 30% CFR PEEK using FEA. They reported that as a result of reduced elastic deformation, CFR-PEEK implant showed decreased stress at the bone-implant interface. Schwitalla et al.[13] compared the titanium, powder-filled PEEK, and Endolign by FEA. According to their results powder-filled PEEK showed higher maximum deformation and stress peaks, while others showed similar stress distributions.

Animal Studies

In an animal study shear strength and bone-implant contact of CFR-PEEK implants uncoated and titanium coated were investigated. The bone-implant contact of the coated implants was found significantly higher.[43] In another experimental study in vivo response of PEEK-HA implants placed into canine tibia was evaluated. The study suggested that bone formation was enhanced with HA adding to PEEK.[44] The effect of nano-HA/polyetheretherketone (n-HA/PEEK)-coated sandblasted, acid-etched (SLA) and large-grit, implants in peri-implantitis model on beagle dog in terms of inflammatory cytokines and osseointegration was explored in another experimental study and findings reveal that this modification can promote osseointegration and relieve the inflammatory response.[45] In a study by Toth et al.[46] PEEK implants were applied in combination with rhBMP-2 or autograft, and they reported to be observed histological integration with sheep bone after 6 months. Xu et al.[47] who prepared Dex/Mino liposome-modified PEEK reported to have improved anti-inflammatory, antibacterial, and osseointegration properties and suggested Dex/Mino liposome-modified PEEK for clinical applications.

Biomechanical Studies

With 4-, 5- or 6-mm diameter, cylindrically shaped PEEK specimens of different PEEK materials (reinforced with continuous carbon fibers, filled with titanium dioxide or barium sulfate powder, reinforced with short carbon fibers or short glass fibers, and unfilled) tested for elasticity and stability in long-term. The results showed that PEEK materials could resist the maximum bite forces.[36]

Clinical Studies

Marya et al.[48] in their clinical study reported three cases of PEEK implants. The implants were prepared with titanium oxide 20 % beta-tricalcium phosphate, and 80 % PEEK. They reported after 6 months of follow-up that PEEK implants have osseointegration potential. However, Khonsaria et al.[49], reported three cases of failed PEEK implants due to severe infection mentioned the poor osseointegration capacity. Mounir et

al.[50] used porous titanium or PEEK sub-periosteal implants rehabilitation of the atrophic maxilla on ten patients and suggest PEEK as an acceptable material.

2.6.2. Trauma and Maxillofacial Reconstruction

Many pathologies and diseases cause deformations in the maxillofacial area. These may cause functional and esthetic problems, and has negative psychological consequences.[51] The restoration of maxillofacial deformities is challenging due to the complex structure of the area and functional and esthetic demands.[52]

Numerous materials have been used in maxillofacial trauma and reconstruction like metal-based biomaterials, methyl methacrylate, bone cement, or polyethylene. All have associated disadvantages like leading foreign body reactions, resulting in infection, failure, poor workability, resorption of the underlying bone, fibrous tissue to grow into the implant, susceptibility of stress shielding and refracture, thermal sensitivity, and artifacts during radiographic evaluation.[53-55] PEEK have become an increasingly popular alternative biomaterial which may mitigate these pitfalls.[56,57] Table 2 shows the clinical applications of PEEK in trauma and reconstruction.

3. Conclusion

PEEK is a modern material that can considered to overcome the pitfalls of the other biomaterials. Due to the excellent mechanical, chemical and physical properties PEEK have become one of the most promising option for most of the applications in maxillofacial surgery. However, the routine usage of this material in the era of maxillofacial surgery especially in dental implantology still needs further evidence and investigation.

Table 2: *Clinical Applications of PEEK in Trauma and Reconstruction*

Kang et al.[58]/2021	39/M	CR	Tumor	Mandible	No	NA
Alasseri et al.[59]/2020	23/F	CS	Parry-Romberg syndrome	Right frontal bone, zygoma, and maxilla	No	18
	28/F		Hemifacial microsomia	Left mandible body and ramus	No	11
	38/F		(BSSO)/large mandibular advancement	Mandibular angles	No	10
	25/M		Fibrous dysplasia	Frontal bone and cranium	No	10
	19/M		Zygomaticomaxillary deformity	Right zygoma and nose	No	12
	50/M		Post mandibular resection	Mandible	No	12
Dessoky et al.[60]/2020	10 (10 M)	P	Body fracture	Mandible	Edema and pain	6
Chepurnyi et al.[61]/2020	28 (7F, 21M)	R	Blowout orbital fractures	Orbita	No	12 (Min)
Saponaro et al.[62]/2020	15 (NA)	P	6- Hemifacial microsomia sequelae 3- Trauma sequelae 3- Plagiocephaly sequelae 3-Demonstrated mandibular imbalance	8- Mandibular angle reconstruction 7-Fronto-orbital reconstruction	No	14 (Avg)
Morsy et al./[63]2019	14 (5M, 9F)	P	Atrophied maxillary alveolar ridge	Maxilla	1-wound dehiscence 1-Sheet exposure	6
Jarvinen et al. [51]/2019	F 23	R	Other specified jaw size anomalies	Symphysis of mandible	No	19
	F 33		Mandibular retrognathism	Symphysis and body of mandible	Minor paresthesia	10
	M 19		Mandibular retrognathism	Symphysis of mandible	Minor paresthesia	3
	F 22		Juvenile rheumatoid polyarthritis	Symphysis of mandible	Minor paresthesia	23
	M 35		Mandibular asymmetry	Symphysis and body of mandible	No	10
	F 20		Mandibular asymmetry	Symphysis of mandible	Minor paresthesia	2

	F 21		Goldenhar syndrome	Angle of mandible	Wound dehiscence	51
	M 23		Other malformation syndrome	Zygomatic bones and lateral orbital rims	Transient facial paralysis	21
	F 26		Mandibular retrognathism	Orbital bones	No	4
	F 24		Orbital deformity (after trauma)	Orbital floor	No	26
	M 72		Fracture of orbital floor	Symphysis of mandible	No	11
	F 49		Mandibular retrognathism	Lateral orbital rim	No	11
	M 20		Apert syndrome	Lateral orbital rim	Early infection	8
	M 21		Crouzon syndrome	Symphysis of mandible	Minor paresthesia	63
	F 20		Hemifacial microsomia	Symphysis of mandible	No	3
	F 49		TMD, Openbite	Zygomatic bone	No	28
	F 22		Achondroplasia, retrognathism	Zygomatic bone	No	10
	F 31		Asymmetry	Orbital floor	No	6
	F 46		Choroid neoplasm, orbital bone absence	Orbital floor and infraorbital rim	No	27
	F 16		Fracture of orbital floor	Orbital floor	No	42
	F 72		Choroid neoplasm, orbital bone absence	Symphysis of mandible	No	3
	M 22		Mandibular retrognathism	Symphysis and body of mandible	No	3
	M 31		Mandibular retrognathism	Symphysis and body of mandible	Minor paresthesia	2
	M 22		Juvenile rheumatoid polyarthritis	Symphysis of mandible	No	2
Mounir et al.[64]/2018	8 (4M, 4F)	P	Atrophied maxillary alveolar ridge	Maxilla	1-wound dehiscence 1-Sheet exposure	6
Patel et al.[65]/2017	51/M	CR	Posttraumatic craniofacial deformity	Zygomatico–maxillary complex	No	4
Powers et al.[66]/2017	15/M	CR	Hemangioma	Zygoma	No	12
Herford et al.[67] /2017	33/F	CR	Post reconstruction infection	Orbital floor	NA	NA

Suresh et al.[56]/2017	8 (6M 2F)	CR	2-Self-inflicted gunshot wounds 1-Crush injury from a horse 2-Motor vehicle collision 2-Private plane crashes 1-Blast injury after tank explosion	2-Reconstruction of the frontal sinus 6-Reconstruction in the maxillary sinus	Infection	0.8
Staal et al.[53]/2016	15/F	CR	Facial asymmetry	Mandibular corpus	No	32
Alonso-Rodriguez et al.[68]/2015	45/F	CS	Craniofacial dysplasia	Frontal bone	No	48
	27/M		Nasopharyngeal Angiofibroma	Zygomaticomaxillary complex	No	43
	21/F		Craniofacial dysplasia	Orbital floor	Infection	27
	26/F		Facial cleft	Zygomaticomaxillary complex	No	28
	53/F		Intraosseous angioma	Frontal bone	CSF leak	20
	45/F		Brain cavernoma	Frontal bone	No	19
	37/M		Odontogenic myxoma	Zygomaticomaxillary complex	No	9
	55/F		Meningioma	Zygomatic and temporal bones	Infection	5
	73/F		Craniofacial dysplasia	Zygomaticomaxillary complex	No	8
	41/F		Trauma	Orbital bone	Sinus inflammation	38
	36/M		Craniofacial dysplasia	Temporoparietal region	Seroma	35
	44/F		Meningioma	Frontoparietal region	No	72
	53/F		Meningioma	Temporoparietal region	Exposure	36
	42/M		Esthesioneuroblastoma	Frontal bone	No	13
Baumann et al.[69]/2015	28/M	CR	Orbital and zygoma fractures	Orbital floor	No	12
Lavie et al.[70]/2015	63/F	CR	Venous malformation zygoma	Zygomatic arch	No	15
Berrone et al.[71]/2015	27/M	CR	Facial asymmetry/major trauma	Mandible	No	8
Gerbino et al.[72] /2015	40/M	R	Osteoma	Cranio-orbital reconstruction	No	18 (Min)
	68/F		Post tumor resection		No	
	72/F		Post tumor resection		No	

	28/F		Post tumor resection			No	
	52/M		Post traumatic deformity			No	
	62/F		Meningioma			No	
	46/F		Hemangioma			CSF leak	
	56/M		Meningioma			No	
	54/F		Meningioma			No	
	46/M		Osteoma			No	
	48/M		Osteoma			No	
	51/F		Meningioma			No	
	54/F		Meningioma			No	
Guevara-Rojas et a. [73]/2014	27/F	Research	Midface hypoplasia	Zygomatic prominence		No	2
Gerbino et al.[74]/2013	54/F	CR	Meningioma	Orbit, sphenoid, temporal, frontal bone		No	31
	56/M		Meningioma	Orbit, sphenoid, temporal, frontal bone		No	29
	46/F		Hemangioma	Orbit, frontal bone		No	25
Jalbert et al.[75]/2012	30/M	P	Osteomeningioma	Frontal bone		No	12
	69/M		Frontal sinus mucocele	Frontal bone, orbital roof		No	12
	61/F		Osteomeningioma	Frontal bone		No	4
	46/F		Osteomeningioma	Fronto-orbito-sphenoidal		No	3
	42/F		Osteomeningioma	Fronto-orbital		No	NA
Scolozzi et al.[76]/2011	29/F	CR	Taruma	Midface		No	24
	29/F		Sliding genioplasty residuel defect	Mandible		No	24
Lai et al.[77]/2011	60/M	CR	Trauma	Fronto-orbito-temporal		No	6
Kim et al.[55]/2009	29/F		Esthesioneuroblastoma	Orbital rim and floor		No	16-20
	19/M		Taruma	Nasal, fronral bone		No	
	11/F		Hemangioma	Forehead and eyebrow		Scar	
	17/F		Trauma	Orbitomaxillary		No	

CR: Case Report, **P:** Prospective, **R:** Retrospective, **CS:** Case Series, **F:** Female, **M:** Male, **NA:** Not Available, **Min:** Minimum, **Avg:** Average

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CHAPTER 10

PERCEIVED STRESSORS, SLEEP QUALITY AND ANXIETY IN THE INTENSIVE CARE UNIT

Merve KARACA[1], Güler BALCI ALPARSLAN[2]

1 ID:0000-0002-4835-3767 Eskişehir Osmangazi University Institute of Health Sciences, Department of Internal Medicine Nursing, Meselik Campus Eskişehir / TURKEY , mrvkrc90@gmail.com
2 RN, MSc, PhD, Prof / ORCID ID: 0000-0003-3734-3843 , Eskişehir Osmangazi University Faculty of Health Sciences, Department of Internal Medicine Nursing Meselik Campus Eskişehir / TURKEY gbalci80@hotmail.com

INTRODUCTION

Intensive care units is defined as " In one or more organs or organ systems aimed at the improvement of patients who need intensive care due to severe dysfunction, placement, format, and the privilege of carrying in terms of patient care, high-tech devices equipped with vital signs and observation of the patient for 24 hours is the clinic where the treatment is performed "(T.C. Sağlık Bakanlığı Genelgesi,2008).

Intensive care units are areas of care where individuals are followed up due to a critical health problem, a multidisciplinary approach is provided to maintain treatment and care, and the hospitalization process is a stressful and difficult environment for the individual and family to cope with.In addition to physical loads, the patient and his relatives have psychosocial problems. The fact that the medical team primarily focuses on physical findings negatively affects the holistic evaluation process of the patient (Şahin&Buzlu,2016;Aydın&Gürsoy,2017; Çam&Küliğ,2018; Olabisi et al,2020).

Florence Nightingale has emphasized the importance of the healing environment in the treatment of patients.It is important to determine the environmental and psychological factors in the intensive care environment that are stressful. Each stressor affects patients' intensive care experiences differently and causes them to experience varying degrees of stress. Detection, elimination and replacement of stressors affecting patients in the intensive care unit positively contributes to the duration of treatment and intensive care stay of patients. The physical, social and psychological health care needs of the patients in these environments should be evaluated and met equally from the holistic point of view (Boz,2018;Gültekin et al,2018;Şahin&Köçkar,2018; Kaçal & Demirsoy,2018; Zengin et al,2020).

PERCEIVED ENVIRONMENTAL STRESSORS IN THE INTENSIVE CARE UNIT

Stress is an adaptive response aimed at restoring body homeostasis and combating environmental problems (Lo Martire et all,2020).The factors that cause stress are called "stressors". A number of psychological, physical and mental negative effects may occur in a person when the stressor is encountered in large amounts and for a long time (Akça Ay, 2019).

Patients in the intensive care unit experience many stressors caused by the characteristics of the environment (Yaman Aktas et al., 2015). It is extremely important to identify, evaluate and eliminate stress factors affecting patients (Abuatiq et al,2015).

A study was conducted in which 42 prospective cross-sectional observational studies were synthesized, in which the perceived stressors in the intensive care unit were examined. In this study, the environmental stressors that patients are most affected by are stated respectively as hearing other patients cry, seeing the operations performed on other patients, hearing the alarms of devices (Krampe et al., 2021).

According to Candan Dönmez et al. (2020) in the study evaluating environmental stressors in the intensive care unit, pain is the first place when looking at the factors perceived as the most stressful, and then, respectively, staying still due to serum sets, unable to drink water, unable to sleep, longing for a partner is included.

Tezcan Karadeniz and Kanan (2019) evaluated environmental stressors in the intensive care unit of reanimation in a study in which the most important stressors that patients perceive were; hearing pain, inability to drink water, meeting with family and friends for a short time, inability to ensure privacy, staying connected to tubes and longing for a partner.

Yaman Aktas et al. (2015) analyzed the environmental stressors perceived by patients undergoing treatment in the intensive care unit of cardiovascular surgery in a study in which the most important stressors were found to be pain, insomnia, loss of privacy and longing for a partner.

In the study conducted by Gencer and Karakoç Kumsar (2020), in which the effect of environmental stressors on sleep quality in intensive care was examined, the factor that was perceived as the most stressful was expressed as the lack of privacy.In the same study, when looking at the causes of sleep problems, nursing and medical care interventions performed during sleep hours, pain and disease-related concerns are included first, respectively.

In a study conducted by Koyuncu et al. (2021) in which the effect of environmental stressors on sleep patterns was examined, it was found that sleep quality was negatively affected as the level of environmental stressors perceived by patients increased.

In a study conducted by Zengin et al. (2020) examining the relationship between environmental stressors in intensive care and intensive care unit experience, it was found that the experiences of patients in intensive care were negatively affected as stressors increased.

INTENSIVE CARE UNIT AND SLEEP

Sleep is a complex physiological phenomenon necessary for growth, repair, cognitive functions, maintenance of life (Chang, Owens, & La Buzetta, 2020).It is characterized as a temporary loss of consciousness,

which can end with stimuli, when cerebral activities decrease to a minimum level during sleep, the creature voluntarily breaks off its relationship with its environment (Saygin & Özgüner, 2020).

Sleep plays an important role in the process of getting rid of acute stress or illness. Sleep deprivation causes negative physiological effects at both the organism and cellular levels (Williams & Naidoo,2020).

The characteristics of the intensive care environment and the presence of critical illness cause sleep disorders in patients. Sleep in the intensive care unit is usually fragmentary, superficial stages of sleep predominate. When looking at the causes of sleep disorders, the acute nature of the disease, patient-specific factors, treatments (mechanical ventilation, medication, etc.) are included. In order to improve the quality of sleep in patients; nursing care practices should include the evaluation and development of interchangeable components of the intensive care environment (Jun et al,2021;Beltrami et al,2015).

According to studies conducted in intensive care patients, the prevalence of sleep disorders was stated to be 22-61%. In these patients, there are changes in sleep patterns characterized by the predominance of the N1 and N2 phases, the decrease or absence of the N3 phase and REM sleep. Patients have a high arousal index, frequent waking up, daytime sleepiness (40-50% of sleep during the day) is observed. Such patients are infrequently able to complete the sleep cycle (Adell et al,2021).

In a meta-analysis conducted by Mattiussi et al (2019), the highest frequency (71.4%) of patients in intensive care as a cause of sleep deprivation was found to be “feeling fear and anxiety”. In this study, 12 codes were created and three main themes affecting sleep quality were expressed. The first of these themes-heard voices, including maintenance activities “to interact with the environment” taking place, while the second act as the inability to move, abandonment, inability to talk, fear, anxiety to feel “which includes encounter with intense emotions and feelings” ,and the third is “ patient care effects ” which include physical pain and feeling insecure of patient.

In a study where sleep assessment was performed in the intensive care unit, a moderate relationship was found between the self-assessments of patients and the sleep assessment of nurses, the nurses’ assessments were higher than the patients’ reports (Aitken et al,2017).

In a study conducted by Elliot et al. (2014) to determine the factors affecting sleep in the intensive care unit, it was found that the patients’ sleep quality was at a poor level, and light and noise were the most influential

factors as the cause of sleep division. In a study conducted by Little et al. (2012) examining intensive care sleep problems, it was stated that the quality of sleep was at a poor level; the most common reasons stated were noise, pain, light, loud speech, and intravenous catheters.

In a study examining the effect of noise on the sleep of patients hospitalized in the intensive care unit, 75% of patients stated that they had sleep problems due to noise. In this study, alarm sounds were expressed as the main factor of noise , and frequent awakenings were analyzed as the most common complaints of patients about sleep (Demir&Öztunç,2017). In the study in which the sleep problems of patients in intensive care unit and the service were evaluated, the causes of sleep problems were stated as noise, pain, coldness of the environment and light, respectively (Uğurlu&Sabuncu,2012).

Adequate sleep is necessary for the recovery process and survival of patients in intensive care (Ortaç Ersoy et al,2016;Hansen et al,2018). Inadequate sleep can disrupt cognitive activities, ranging from apathy and confusion to delirium. It also affects tissue repair and cellular immune function, potentially changing the recovery time. Long-term insomnia and the accompanying stress response initiate the permanent production of pro-inflammatory cytokines, causing chronic low-grade inflammation and immunodeficiency (Pulak & Jensen,2016).

INTENSIVE CARE UNIT AND ANXIETY

The intensive care unit, where advanced technology is used, causes sensory changes in patients due to an excess of environmental stimuli, intensive treatment and care, lack of social support (Uzelli&Korhan,2014).

Anxiety can be defined as a stimulating signal, similar to fear, expressed by patients as an internal distress. This signal ensures that the necessary measures are taken to overcome any threat element. Fear is felt when faced with a threat from the outside, while anxiety occurs when there is a conflict from the inside. When anxiety occurs in a person, signs such as palpitations, dry mouth, mydriasis are observed in order to escape from the situation (Tamam&Demirkol,2019).

Anxiety occurs in 70-80% of intensive care patients, especially in the majority of patients followed up on mechanical ventilator support (Adsay,2015). Symptoms of depression, anxiety, post-traumatic stress disorder can often be observed in patients in the intensive care unit. Similar symptoms can also be encountered near the patient. Medical staffs play an important role in the early detection of psychological problems of the patient and patient’s family,the identification and elimination of the

underlying causes (Castillejos et al,2021; Lebel et al,2021). Lengthening of stay in intensive care has been associated with more negative experiences (Bani Hani et al,2021).

In the study conducted by Gerkuş and Yıldız (2020), in which the effect of environmental stressors in intensive care on anxiety levels was examined, it was found that environmental stressors significantly increase anxiety. Rattray et al. (2010) examined the anxiety and post-traumatic stress status of patients discharged from the intensive care unit in a study that found a positive relationship between the intensive care stressors and their psychological status of patients.

Sedation is frequently used in the intensive care unit to reduce agitation, anxiety and pain of patients, prevent patient-ventilator incompatibility, invasive procedures, facilitate aspiration applications, etc. In the studies conducted, a minimum level of sedation is recommended, during which the patient's comfort and safety in the environment will be ensured. Close monitoring of the patient receiving sedation is required (Tel Aydın &Çelik,2017; Doğanay &Sezer Akman,2018).

People with anxiety and anxiety-related disorders generally have poor sleep quality, sleep disorders are observed, especially insomnia. At the same time, insufficient sleep can provoke anxiety or exacerbate it. Individuals with sleep disorders should be evaluated in terms of anxiety; individuals with anxiety should be evaluated in terms of sleep disorders (Chellappa & Aeschbach,2021).

CONCLUSIONS

Patients in the intensive care unit are in constant interaction with the environment and experience more stressors than in other areas. It is the main task of nurses to ensure the early detection and management of environmental stress factors in these environments. Stressors cause sleep disorders and anxiety in patients. This situation affects negatively the process of recovery and treatment of patients.

Intensive care nurses should be able to identify the environmental stressors that patients face, be aware of sleep and anxiety problems, and in this direction, increase their adaptation to the environment, regulate their care activities. Holistic evaluation of patients in terms of creating a remedial care environment will improve the quality of treatment and care provided.

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CHAPTER 11

INSULIN

Sabrina AZI MOHAMEDa[1], Birgül KURAL[2]

1 BBiochem, haloumkatabi@gmail.com, 0000-0001-8473-1801 Department of Medical Biochemistry, Graduate School of Health Sciences, Karadeniz Technical University, 61080, Trabzon, Turkey
2 Prof. PhD., bvanizorkural@ktu.edu.tr, 0000-0003-0730-9660 Department of Medical Biochemistry, Faculty of Medicine, Karadeniz Technical University, 61080, Trabzon, Turkey

1. History of Insulin

Insulin's history can be divided into three eras: pre-era, insulin-era, and post-insulin era, which scientists still debate. Long before the discovery of insulin, diabetes has been a major and very dangerous disease. In the pre-era, each civilization had its own of trying to cure diabetes without understanding its source. Physicians like Pierre Adolphe Piorry in the 1850s believed that hyper-caloric diets could compensate for the urinary loss of calories. Nevertheless, other physicians became aware that hypo-caloric diets were better at boosting diabetes symptoms later on. In this era, the best to cooperate with diabetes was to eat less food. Insulin discovering history is part of understanding the functioning of the pancreas. The pancreas is a composite organ named by the Greeks meaning, "All flesh". Paul Langerhans, a German pathologist, physiologist, and biologist, in 1869 became the first person to identify the pancreas's stem cells. In 1921, Best, Banting, Mcleod, and Collip were able to discover insulin molecule *(Vecchio et al., 2018).* In 1936, Harold Percival Himsworth was the first to identify the difference between insulin-sensitive and insulin-insensitive in diabetes mellitus and was able to develop the first test to quantify insulin sensitivity *(Kim et al., 2011). In 1969,* Dorothy Crowfoot Hodgkin presented the structure and contributed an anatomic model of insulin molecule *(Glusker et al., 1994).* Robert Tattersall and Stephen Fajans presented the monogenic forms of diabetes in 1982. In 1978, David Goddel and his colleagues contributed the first recombinant DNA human insulin. The researches on insulin are still ongoing *(Quionzon et al., 2012).*

2. Insulin Biosynthesis

The pancreas is composed of a head, body, and tail sited near the duodenum. The pancreas is a composite organ located in the back of the peritoneum. This organ's mass consists of approximately 90% of exocrine cells placed in lobules and divided by connective tissue *(English et al., 2019).* The endocrine cells from the Islets of Langerhans secrets one of the most important hormones such as insulin, glucagon, and somatostatin *(El Sayed et al., 2021).*

The human insulin gene is located on chromosome 11. The biosynthesis of insulin begins with mRNA translation to preproinsulin (a single chain with 110 amino acids). As soon as the posttranscriptional peptide enters the endoplasmic reticulum the signal peptide is ejected by signal peptidase enzyme, as a result transforming preproinsulin to proinsulin (has a carboxy-terminal A chain, an amino-terminal B chain, and a C peptide). In the endoplasmic reticulum, three disulfide bonds are formed between cysteine residues by protein disulfide isomerases. Two disulfide bridges connect B and A chains. Proinsulin shifts from the endoplasmic reticulum to the golgi

organelles and secretory granules. The splinter of the C-peptide in this section transforms proinsulin into mature insulin composed solely of the B and A chains. Also, carboxypeptidase E/H protein convertase 1/3 (PC1/3) comes into play to form mature insulin. Secretory granules are the final destination of the mature insulin, which is stored until the fusion between granules and plasma membrane to discharge insulin. Approximately $>3\times10^3$ new insulin molecules are produced per second per β-cell. Zn^{2+} non-covalently attaches to His B10 to make the insulin hexamer *(Vasiljević et al., 2020).*

3. Insulin Structure

Insulin is a polypeptide and a main anabolic hormone that is produced by the pancreas β-cells. It is active as a monomer. This hormone has a molecular weight of 5808 Da with 51 amino acids residues. The human insulin is composed of two polypeptide chains (A chain and B chain, consisting of 21 and 30 amino acid residues, respectively). Two disulfide bridges connect B and A chains between cysteine residues (CysA7-CysB7 and CysA20-CysA19). There is a third bridge connecting the cysteine residues in the A chain (CysA6-CysA11) *(Mao et al., 2019).*

The half-life of insulin is around 3-10 minutes. Insulin formation depends on the conditions of media such as the metal ions and pH. Moreover, the charge and solubility of the insulin are affected *(Dağaşan et al., 2020).*

4. Insulin Secretion

Insulin secretion is a mechanism related to the response of an elevation of blood glucose. The secretory process is divided into two phases, the first phase also known as the fast phase can continue up until 15 minutes and the second phase can last about 30 minutes or more. The rapid secretion of a total of 40-80 LDCV's (large dense-core vesicles) per β-cell is believed to be the cause of the initial phase *(Barg et al., 2004).* The initial phase, known as the triggering phase, entails different steps resulting in the secretion of insulin. The triggering starts with the entry of glucose by facilitated diffusion, then the glucose is metabolized by oxidative glycolysis which causes the elevation of the ATP/ADP ratio that leads to the shutting down of the ATP-responsive K^+ (K^+_{ATP}) channels. The closure of K^+_{ATP} channels generates membrane depolarization that initiates the unlocking of voltage-operated Ca^{2+} channels. The exocytotic machinery is started by the increasing cytoplasmic free Ca^{2+} concentration *(Henquin et al., 2000).*

The amplifying pathway is also known as the K^+_{ATP}-independent pathway, a metabolic amplifying relay on the initial triggering pathway to affect insulin secretion. Receptors present in the β-cell membrane unite

with neurotransmitters and various hormones, leading to neurohormonal amplifying pathways that enhance nutrient-induced insulin secretion *(Henquin et al., 2000).*

Glutamate dehydrogenase (GDH) is present in an essentially anaplerotic/cataplerotic pathway, which contains the tricarboxylic acid cycle that is recharged or provides carbons and intermediates for amino acid metabolism *(Plaitakis et al., 2017)*. Moreover, glutamate dehydrogenase uses leucine amino acid as an allosteric activator. Leucine plays an important role in the stimulation of insulin secretion. Leucine triggers insulin secretion in two ways; first by the direction of deamination to submit α-ketoisocaproate, and second, to increase glutaminolysis by allosterically initiating glutamate dehydrogenase, an important enzyme for the control of the oxidation of glutamate *(Yang et al., 2010).* Glutamate dehydrogenase once activated is responsible for the deamination of glutamate to α-ketoglutarate using either NAD^+ or $NADP^+$ as a redox coenzyme. Thus, α-ketoglutarate elevation in the mitochondria leads to an increase in ATP production throughout respiration. The augmentation in the cytosolic ATP/ADP ratio ultimately triggers the shutdown of K^+_{ATP} channels, leading to plasma membrane depolarization and the influx of Ca^{2+} ions. Increased intracellular Ca^{2+} levels precipitate insulin secretion *(Göhring et al., 2012).*

The isocitrate dehydrogenase pathway is essential to the contribution in the amplification of signals for glucose-stimulated insulin secretion (GSIS) *(Campbell et al., 2021).* IDH1 and IDH2 are homodimers, which are responsible for the decarboxylation of isocitrate to 2-oxoglutarate *(Zahnow et al., 2019).* The isocitrate-IDH1/IDH2 pathway is crucial in the amplification of the signals for the GSIS secretory system through a process requiring the NADPH-navigated reduction of glutathione by glutathione reductase. The reduced glutathione initiates glutaredoxin, which is a small ubiquitous oxidoreductase enzyme responsible for the transfer of electrons from NADPH to disulfide substrates. The activation of sentrin/SUMO-specific protease 1 (SENP1) starts with the reducing of cysteine disulfides by glutaredoxin. SENP1 works as a demoSUMOylase, which extracts SUMO peptides from secretory granule-trafficking proteins such as the Ca^{2+}-sensing protein synaptotagmin VII to intensify exocytosis of insulin from granules *(Campbell et al., 2021).*

Free fatty acids (FFAs) have an enhancing property on glucose-stimulated insulin secretion (GSIS). Long-chained unsaturated fatty acids are considered the most effective secretagogues for insulin. The FFAs take action along FFA receptor 1 (FFAR1), a highly expressed G-protein-coupled receptor in β-cells. FFAs binding to FFAR1, initiate

the phospholipase C (PLC)-mediated hydrolysis of phosphatidylinositol 4, 5-biphosphate to make diacylglycerol (DAG) and inositol triphosphate. DAG induces protein kinase C. However, inositol triphosphate induces Ca^{2+} ions secretion coming out of the endoplasmic reticulum. Moreover, the interaction of FFA-FFAR1 generates the activation of protein kinase 1 by DAG. Protein kinase 1 initiates the remodeling of the cortical F-actin and recruits the secretory granules for insulin exocytosis *(Campbell et al., 2021).*

The glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP1) are both hormones that trigger insulin secretion in a glucose-dependent way and are therefore known as incretin hormones. GIP secretion is stimulated in response to nutrient intake *(Mclntosh et al., 2009).* GIP affects both β-cells and α-cells and is involved in direct and indirect insulin release respectively. GIP interacts with the GIP receptor (GIPR) resulting in insulin release via cyclic adenosine monophosphate (cAMP)-dependent mechanisms. GIP triggers amino acids in α-cells, which activates glucagon secretion. Insulin negatively modulates glucagon production and glucagon usually opposes insulin action. Moreover, α-cells and glucagon produce GLP1 via a substitute pathway of the proglucagon peptide precursors. Insulin and glucagon elevate the concentration of cAMP in β-cells to modulate insulin production following a meal. Hence, GIP's incretin-like action promotes insulin secretion directly on β-cells and indirectly on alpha cells, occurring by the paracrine inciting effects of proglucagon-derived peptides. Urocortin 3 (UCN3) is a product of beta cells that stimulates a different action of paracrine effect in the islet. UCN3 incites epsilon cell activity to elevate somatostatin production via the corticotropin-releasing hormone receptor. Increased levels of somatostatin inhibit the secretory activity of β-cells, finalizing a negative feedback loop *(Campbell et al., 2021).*

NO is found in three different isoforms and has a ubiquitous signal potential. Neuronal nitric oxide synthase (nNOS) is mostly found in insulin secretory granules and also at lower levels in the mitochondria and the nucleus. Even though endothelial NOS (eNOS) is present in pancreatic β-cells but the data on its function in beta cells is lacking. At elevated glucose levels, inducible NOS (iNOS) is expressed in the endoplasm. However, in β-cells iNOS is undetectable at the lowest glucose levels. One of the most critical steps for glucose-stimulated insulin secretion is the mobilization of Ca^{2+} that is triggered by an endogenous nNOS-derived NO at physiological levels. The mobilization of Ca^{2+} begins from the endoplasmic reticulum to the mitochondria, which elevates the free Ca^{2+} concentration. Moreover, nNOS-derived NO triggers S-nitrosylation

of glucokinase, which is an essential element of insulin particles and modulates its location and activity. In elevated concentrations of glucose, nNOS-derived NO might react as a negative feedback signal for glucose-stimulated insulin production by triggering the K^{+}_{ATP} channels. The toxic concentration of glucose of inflammatory cytokines causes pathological concentrations of iNOS-induced NO that leads to disarrangement of the glucose-stimulated insulin secretion, thus interrupting the glycolytic pathway and mitochondrial respiration *(Bahadoran et al., 2019).*

In addition to the above-mentioned contributors, Vitamin D also contributes to insulin secretion by increasing the calcium level *(Kjalarsdottir et al., 2018).*

5. Circadian Regulation of Insulin

The primary controller of the circadian system is known as the suprachiasmatic nucleus *(Welsh et al., 2010).* As the day progresses insulin secretion and peripheral insulin action decrease. The liver clock, before sleep, may increase gluconeogenesis to maintain blood glucose homeostasis *(Poggiogalle et al., 2017).* Brain-derived melatonin increases in humans in the evening and prepares β-cells to secrete insulin in response to glucose in the morning. The β-cells are responsible for the coordination of blood glucose concentrations throughout the diurnal cycle for the brain and peripheral insulin-sensitive tissues *(Perelis et al., 2016).*

6. Insulin Effects

It has been acknowledged that insulin is a hormone, which has different types of effects such as rapid, intermediate, and delayed. Insulin has a rapid effect that can lead to elevated transportation of glucose, amino acids, and K^{+} into insulin-sensitive cells. In addition, insulin acts as a stimulator of protein synthesis, activator of glycolysis, glycogen synthesis, and inhibitor of gluconeogenesis. Moreover, insulin has a delayed effect that leads to an increase in the mRNA of lipogenic and other enzymes *(Hameed et al. 2016).* Furthermore, insulin acts as a regulator of the different physiological processes such as the metabolism of lipid, protein, and glucose, the neurohormonal activity, the cell cycle, growth and survival, the exchange or transport of ions and amino acids, the vascular tone, and inflammation *(Mancusi et al., 2020).*

It is accepted that insulin is a molecule, which goes through rapid non-enzymatic covalent conjugation with glucose or various sugars. The insulin receptor is composed of regions similar to insulin, which are linked with both glucose and insulin binding. In hyperglycemic conditions, both insulin receptor and insulin may be glycated. Thus, the binding between them may not take place *(Rhinesmith* et al., 2017).

7. Insulin Receptor

The insulin receptor was first characterized to be in the class of the tyrosine kinases receptors in 1971 *(Polidori et al., 2021).* Its gene is positioned on chromosome 19. It has 22 exons and 21 introns *(De Meyts et al., 2016).* Insulin receptor goes under alternative splicing and initiates a pair of elementally distinct isoforms known as insulin receptor-B (IR-B) and insulin receptor-A (IR-A). IR-A is majorly expressed in embryonic and fetal tissues, hematopoietic cells, cancerous cells, while IR-B is mostly in the main insulin affecting tissues such as fat, muscle, and fat *(Vella et al., 2018).*

This receptor is a heterotetrameric glycoprotein with a pair of extracellular α and a pair of transmembrane β-subunits linked by disulfide bonds. The α-subunits contain insulin-linking sites. The β-subunits carry tyrosine kinase activity *(De Meyts et al., 2016).* Once released insulin attaches to the specific membrane-bound insulin receptors located on the target cells and this will lead to the starting of the metabolic process in these cells *(Primavera et al., 2020)*. Thereby, Insulin can elevate glucose uptake, glycogen synthesis, lipogenesis, protein synthesis, gene expression, DNA synthesis, amino acids uptake, (Na^+K^+)-pump. In addition, insulin acts as an inhibitor in pathways such as gluconeogenesis, lipolysis, apoptosis, and autophagy *(De Meyts et al., 2016).*

8. Insulin Resistance

Insulin resistance is described as the lack of response of target tissues like liver, muscle, adipose, which causes as compensatory feedback an elevated amount of insulin secretion also known as hyperinsulinemia *(Srinivason et al., 2022).* An elevation of the insulin concentration and glucose in the plasma leads to insulin resistance even before any appearance of symptoms *(Lian et al., 2022).*

Insulin resistance can also be called the dysregulation of insulin signaling pathways. It can cause different kinds of diseases such as obesity, diabetes, coronary heart disease, hypertension, and other conditions distinguished by metabolic syndrome. High insulin levels may lead to a reduction in the concentration of insulin receptors on the cell surface, reduced activity of insulin receptor tyrosine kinase, and suppression of downstream signaling proteins analogous to phosphoinositide 3-kinase (PI3K) and protein kinase B of modification in intracellular metabolic pathways that make them less sensitive to insulin *(Tomar et al., 2022)*. Insulin resistance may be caused by a deficiency in insulin signaling *(Lee et al., 2022).*

Insulin resistance is mostly evaluated by different methods hyperglycemic-euglycemic glucose clamp and glucose tolerance methods

are some of the most valid methods *(Gutch et al., 2015).* The homeostasis model assessment (HOMA) method uses two equations for analyzing the β-cells activity and IR *(Lian et al., 2022).* Precise evaluation of insulin resistance in children is tricky, because of various factors such as physical activity, diet, pubertal state, and menstrual cycle, which can affect the stability between glucose homeostasis and pancreatic β-cell function *(Polidori et al., 2021).*

9. Insulin Resistance and Covid-19

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is an infectious virus wrapped in a positive single-stranded large RNA that eventually causes coronavirus disease-2019 (Covid-19), which can trigger severe fatal symptoms such as organ failure and pneumonia *(Velavan et al., 2020)*. Angiotensin-converting enzyme 2 (ACE2), the enzyme responsible for regulating blood pressure by converting angiotensin 2 to angiotensin (1-7)) is the main known receptor for SARS-CoV-2 *(Mahmudpour et al., 2022).* This receptor is also expressed by the endocrine and exocrine pancreas cells *(Govender et al., 2021).* It reduces insulin resistance, oxidative stress and enhances glucose transporter 4 (GLUT4) function *(Mahmudpour et al., 2022).* Binding of SARS-Cov-2 to ACE2 results in pancreatic destruction. This situation increases diabetes and complications. However, during SARS-CoV-2 infection, ACE2 expression is reduced. This causes pathological conditions due to the increase of angiotensin 2. Downregulation of ACE2 triggered by SARS-CoV-2 destroys β-cell function. In other words, SARS-CoV-2 triggers the disparity in ACE2/renin-angiotensin system (RAS) signaling, insulin sensitivity, and hyperglycemia, resulting in cardiovascular diseases and β-cell dysfunction *(Srivastava et al., 2022).* Insulin resistance cooperates with hyperinflammation, intensifying the hyperactive immune response and increasing the weight of the virus after infection. It has been postulated that >90% of the cells responsible for insulin secretion are damaged, thus resulting in non-autoimmune diabetes after a viral infection. In addition to the non-specific activation of the immune system, Covid-19 also causes the secretion of many cytokines, which triggers insulin resistance and hyperglycemia *(Unnikrishnan et al., 2021).* Since SARS-CoV-2 can directly affect the pancreatic β-cells, insulin resistance is seen in the patients during Covid-19 infection. Diabetic patients need much higher doses of insulin *(Mahmudpour et al., 2022).* However, the patients treated with insulin may show a higher risk of mortality and intensive care unit admission *(Yang et al. 2021).*

10. Insulin and Brain

Insulin acts on the brain mainly via a receptor-mediated transport system *(Blázquez et al., 2014).* Furthermore, the locally synthesized insulin takes place inside the cerebral cortex. Insulin originating from

neurons is in charge of the speedy regulation of synaptic mechanisms and microcirculation. Moreover, neuronal insulin affects the energetic homeostasis of neural networks *(Agrawal et al., 2021).* It is believed that locally made insulin has an effect on such as neuronal metabolism, neuronal development, synaptic efficacy, neuronal firing, food intake, reproduction, neuronal survival, memory, and cognition. *(Csajbók et al., 2016).* An experiment on rabbits has confirmed that insulin gene 2 (INS2) is expressed inside the neurons of the hippocampus and olfactory bulb. Hippocampal granule cells taken from adult rats and neuronal progenitor cells originating from the hippocampus of the olfactory bulb can express insulin mRNAs. On the other hand, the expression of Ins2 was detected inside the cortical and subcortical areas of the mouse brain. INS mRNA expression is found for human specimens at hippocampus, olfactory bulb, cerebellar, and pontine regions *(Csajbók et al., 2016).*

The intranasal insulin administration method allows the distribution of insulin to the central nervous system in the relative absence of systemic uptake and associated peripheral side effects. This method is believed to transfer insulin throughout the olfactory and adjacent pathways and has been demonstrated to rapidly assemble in cerebrospinal fluid, showing efficient transport to the brain. Applications of intranasal insulin affect functionally the metabolisms such as reducing nutrition consummation and body weight, ameliorating glucose homeostasis, and improving cognition and memory *(Hallschmid et al., 2021).*

11. Insulin Degrading Enzyme

Insulin endosomal degradation takes place with three proteases such as cathepsin D, neutral arginine amino-peptidase, and insulin-degrading enzyme. Cathepsin D is responsible mostly for proteolytic degradation within endosomes. Neutral arginine amino-peptidase is an enzyme that acts on arginine (Arg) residues. The Arg-A0 human insulin peptide is very responsive to the activity of the protease mentioned above *(González-Casimiro et al., 2021).*

The insulin-degrading enzyme (IDE) was discovered about 70 years ago and named insulinase (which means that inactivates insulin) *(González-Casimiro et al., 2021).* It has a molecular weight of approximately 118 kDa. IDE is ubiquitously expressed in insulin-responsive and non-responsive cells. It is highly found in the brain, liver, kidney, and muscles. It is mostly a cytosolic enzyme. In addition, it can be located in the endosome, peroxisome, mitochondria, plasma membrane, endoplasmic reticulum, exosome, and cerebrospinal fluid. Human IDE is produced as a single polypeptide and contains about 1019 residues, encoded by a gene positioned in chromosome 10. It is composed of two halves, IDE-N and

IDE-C, and each contains catalytic residues and contributes to the binding of substrate respectively. IDE-N and IDE-C halves serve for substrate attachment. Each halves could spin from each other causing extended and locked conformation, which gives permission or denies entry of substrate *(Fernández-Gamba et al., 2009).*

IDE is also known as insulysin, insulin protease, insulin-glucagon protease, neutral thiol protease, metalloendoprotease (Zn^{2+}-metalloprotease), amyloid-degrading protease, and peroxisomal protease *(Fernández-Gamba et al., 2009).* IDE degrades insulin following some steps. Firstly, insulin binds to the insulin receptor, which causes autophosphorylation of the receptor. The insulin- receptor activates tyrosine and the rest elements of the cascade will later be activated. The entry of glucose leads to glycogen synthesis and elevation of mitogenesis. The insulin and insulin-receptor-bound component enters the endosome and will be degraded. IDE is also responsible for the elevation of proteasomal activity *(Fawcett et al., 2009).* pH impacts on cellular media and affects the activity and conformation of IDE *(Grasso et al., 2015).* IDE in synergy with the mitochondrial protein sirtuin 4 can modify IDE protease action via ADP-ribosylation. FFAs and nucleotide triphosphates suppress insulin-degrading action, while reproductive steroids induce IDE expression. Inactive cellular insulin is degraded by endosomal IDE *(Hamel et al., 2003).* The resulting insulin fragments are broken down into amino acids by lysosomal proteases such as cathepsin D. In diabetic individuals, IDE levels in the cytosol are low due to zinc deficiency *(Song et al., 2016).*

The inhibition of IDE activity may cause the elevation of insulin, glucagon, amylin, and β-amyloid levels. The elevation of insulin concentration leads to glucose resistance. Elongated hyperinsulinemia can trigger the breakdown of insulin resistance. The augmentation of insulin is thought to be responsible for the elevation of proliferation, which facilitates cancerogenesis. Elevated postprandial glucagon may cause liver hyperglycemia and activate gluconeogenesis. In the pancreas, amylin concentration gets elevated, which triggers the formation of toxic oligomers, amyloid-beta monomers in the brain, thus causing neuroinflammation, apoptosis, and function disturbances *(Pivovarova et al., 2016).*

It has been deduced that IDE has a different type of substrate with different K_M values. The imbalance of substrate can influence the degeneration of the activity of IDE and hence cause the pathogenesis of Alzheimer or type 2 diabetes. Consequently, if the amount of insulin inside the brain increases, it prevents IDE from breaking down amyloid-beta effectively, which can cause amyloid-beta neurotoxicity and subsequent Alzheimer. Both insulin and its receptors may be part of the synaptic conductance inside the brain and have a responsibility in actions such

as learning and remembering. Moreover, in a normal brain, they both go down with aging *(Qiu et al., 2006).*

12. Insulin Clearance

Endogenous insulin has halftime of 6 minutes and it can be cleared from circulation between 10-15 minutes *(Pecoit-Filho et al., 2016).* In addition to the liver, the kidney is known to be a highly important organ for insulin clearance. Insulin degradation is mostly (50-70 %) made by specialized machinery of internalization and degradation *(Pina et al., 2020).* Insulin goes through hepatic and extrahepatic clearance *(Piccinini et al., 2020).* Following the liver clearance, the remaining free insulin in circulation (30-50 %) is broken down by the kidney. Since insulin is a small molecule, it is completely filtered by the glomerular system until it arrives in the proximal tubule. In the proximal tubule cells, nearly all filtered insulin will be taken up into the luminal membrane. Under physiological conditions, solely a slight percentage is discharged with the urine *(Pina et al., 2020).* There are two pathways; insulin uptake by proximal tubular cells via glomerular filtration followed by endocytosis. It is linked to the diffusion of insulin from the peritubular capillaries and their link to the contra luminal tubular membrane, in particular from the distal part of the nephron *(Pecoit-Filho et al., 2016).* Insulin supplied by the distal half of the nephron initiates various important processes such as the intake of sodium, phosphate, and glucose. In addition, insulin distributed to proximal tubular cells is reduced to oligopeptides and amino acids by one of two roughly described enzymatic pathways *(Rabkin et al., 1984).* Thus, insulin is transferred by lysosomes and metabolized into amino acids liberated by diffusion in the peritubular vessels, and then the final products of degradation are reabsorbed *(Pecoit-Filho et al., 2016).* Insulin is reabsorbed by the renal epithelial cells, which requires saturable linking to low-affinity high-capacity sites at the brush border membrane that is revealed to probably be scavenger receptors like megalin, and cubilin (known as protein, which redeems various proteins by endocytosis). Approximately a small amount of insulin is eventually eliminated in urine *(Duckworth et al., 1998).*

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CHAPTER 12

THERAPEUTIC EFFECTS OF GINKGO BILOBA EXTRACT IN NEUROPSYCHIATRIC DISORDERS

İpek DUMAN[1], Çiğdem GÖKBAŞ EKEN[2]

1 Asst. Prof., MD, PhD. Necmetin Erbakan University, Meram Faculty of Medicine, Department of Medical Pharmacology, Konya. ORCID: 0000-0002-0079-6374
2 MSc. 41th Family Health Center, Karatay, Konya. ORCID: 0000-0002-6474-9745

1.GINKGO BILOBA

Ginkgo biloba extract (EGb 761) is currently one of the most widely used substances in treating Alzheimer's disease. EGb-761 is extracted from Ginkgo biloba tree leaves. The extract contains 24% flavonoids and 6% terpenoids (Zhou et al., 2004). The extract has been widely studied and used to remedy neuropsychiatric disorders and peripheral vascular diseases (Smith & Luo, 2004). This chapter summarizes the pharmacological properties of EGb-761 and evidence relating to the therapeutic effects of EGb 761 in neuropsychiatric disorders in experimental and clinical studies.

The Chinese have used Ginkgo biloba in medicine for over 5,000 years to treat asthma, cough, and enuresis (Bilia, 2002). Most commercially available Ginkgo biloba extracts are made by standardizing the flavonoids or terpenoids in the leaves by enriching them with water-acetone or water-ethanol (Bilia, 2002). The extract contains 24% flavonoids and 6% terpenoids (Zhou et al., 2004). Ginkgo biloba products have become popular in the world market. Adusumilli et al. (2004) showed that nearly two billion daily doses of EGb-761 extract had been sold in recent years. According to Germany's legal health insurance system, in 2008, 7.4 million doses of EGb-761 extracts were used daily, but their actual use is probably higher because it is sold without a prescription (Schwabe & Paffrath, 2013).

1.1 Constituents of Ginkgo Biloba

Ginkgo biloba contains terpenoids and flavonoids, two different substances groups. Also, it contains alkylphenols, polyprenols, and organic acids (van Beek & Montoro, 2009). Ongoing research focuses on ginkgo leaves' therapeutic values, the main components listed in Table 1 (Tian et al., 2017). Standardized EGb-761 extract contains 22-24% flavonoids and 6% terpenoids, and <5 ppm ginkgolic acid (Nakanishi, 2005) (Table 1).

Table 1: The main chemicals of Ginkgo biloba

Class	Chemical Constituents
Terpenoids	Diterpenes Ginkgolides A, B, C, J, M, N, K, L
Flavone, flavanol glycosides, aglycones	Quercetin Kaempferol Isorhamnetin Luteolin Rutin Apigenin Myricetin
Dihydrogen flavonoids	Aromadendrin 5,7,4 trihydroxy-flavone
Polyprenols	Di-trans-poly-cis-octadecaprenol
Organic acids	Ginkgolic acid

1.1.1 Terpenoids

Terpenoids, which are components of Ginkgo biloba, are the only natural product that contains only one tertiary-butyl group in its structure. Terpenoids are present 6% in EGb 761. It contains 3.1% ginkgolide and 2.9% bilobalide (Rojas et al., 2016).

Decreases in mitochondrial function play an important part in Alzheimer's disease (Eckert et al., 2005; Abdel-Kader et al., 2007; Leuner et al., 2007; Mancuso et al., 2007). Terpenoids protect the mitochondria from damage that occurs with aging and improves mitochondrial energy metabolism. There are two possible mechanisms for mitochondrial protection with EGb-761 (Müller et al., 2009):

1. The receptor antagonism of platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) (Belayev et al., 2008).

PAF has potent phospholipid mediator effects on the functioning of leucocytes, aggregation of platelets, and pro-inflammatory signaling. Excessive PAF increases neuronal damage. Because terpenoids act as PAF antagonists, they inhibit neuronal damage and play a crucial role in preventing ischemic brain injury (Smith & Luo, 2004; Chen and Bazan, 2005; Ramassamy et al., 2007; Belyaev et al., 2008).

2. Interaction with chloride channels (Chatterjee et al., 2003; Klein et al., 2003).

Terpenoids selectively block the glycine-activated-chloride-channel in hippocampal neurons of rats (Chatterjee et al., 2003). As a result, terpenoids are known to have a variety of biological activities such as peripheral vasoregulation, platelet-activating factor receptor antagonism, neuroprotection, and free radical scavenging (Huang et al., 2014). They can also protect from impairment in learning and memory.

1.1.2 Flavonoids

Flavonoids are considered polyphenolic compounds with a 15-C atom, 2-phenyl benzopyrone (diphenyl propane) structure (C6-C3-C6) found in various plants (Kahraman et al., 2002).

Flavonoids are present 24% in EGb-761 extract (Rojas et al., 2016). Flavonoids show their effectiveness by preventing the formation of ROS [reactive oxygen species (radicals): singlet oxygen ($^1O_2$), superoxide anion (O_2^-), hydroxy (OH^-), peroxy (ROO^-) and alkoxy (RO^-)] or clearing ROS (Husain et al., 1987; Bors et al., 1990; morel et al., 1993). Moreover, flavonoids alter antioxidants' expression and chelate pro-oxidant transitive ions (Morel et al., 1993). Flavonoid fractions in EGb-761 extract (e.g., Kuersetin) have been shown in some studies to have higher radical inhibitory potential than terpenoids (Ahlemeyer & Krieglstein, 2003; Smith & Luo, 2004; Ramassamy et al., 2007).

In the hippocampus, flavonoids interact with neuronal receptors and modulate gene and protein expression, which controls kinase signaling pathways transcription factors, affecting memory and learning processes (Rendeiro et al., 2012). As a result, memory, learning, and cognitive function are improved due to enhanced cerebrovascular blood flow and synaptic plasticity (Rendeiro et al., 2012).

It is suggested that large quantities of flavonoid intake have protective effects on cardiovascular diseases (Hertog et al., 1997; Yochum et al., 1999). Moreover, flavonoid glycosides are considered effective in treating chronic venous insufficiency (Wurglics & Schubert-Zsilavecz, 2006). In addition, some flavonoids are claimed to preserve natural immune cell function (Rubio-Perez & Morillas-Ruiz, 2012). Some studies show that by reducing inflammatory cytokine production, they reduce signaling in particularly TNF-α (tumor necrosis factor-α), IL-1β (interleukin-1β), prostaglandin E_2 and NF-kB (nuclear factor kappa-B) (Ude et al., 2013).

1.1.3 Ginkgolic Acids

Ginkgolic acids are N-alkyl phenolic acid compounds. They may be responsible for severe allergic reactions (Ude et al., 2013). In addition, they are also considered to be cytotoxic, mutagenic, genotoxic, and carcinogenic (Liu & Zeng, 2009). Due to the allergenic property German Ministry of Health Commission requires ginkgolic acids to be less than five ppm in Ginkgo preparations (Blumenthal, 1999; Blumenthal et al., 2000).

2. GINKGO BILOBA AND NEUROPSYCHIATRIC DISORDERS

EGb-761 has been used for centuries to treat various diseases (Zhou et al., 2004). Today, Ginkgo leaf extracts are sold as oral liquids, film-coated tablets, or readily injectable solutions (Chan et al., 2007). Studies have been conducted on the bioavailability and pharmacokinetics of this extract's components, which are so widely used.

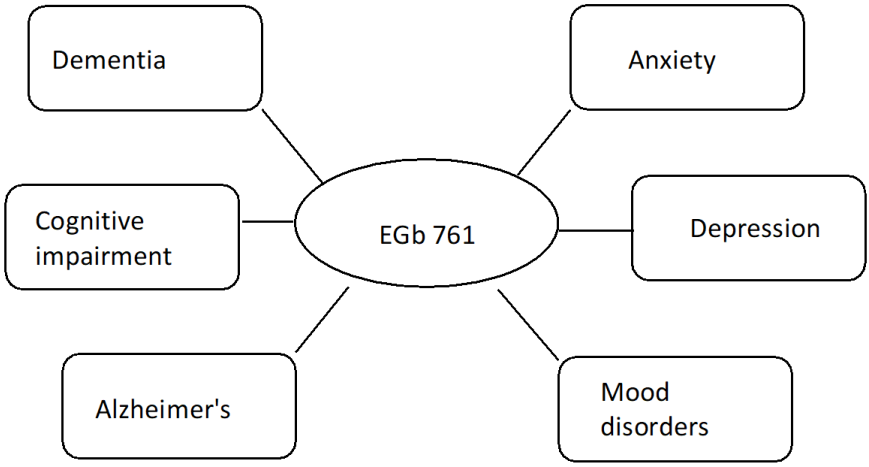
Studies on the pharmacokinetics of orally consumed EGb-761 extract have shown that flavonoids are absorbed in the intestine and metabolized by the flora (Kressmann et al., 2002).

The EGb-761 extract is currently used in Phytotherapy as an alternative drug to prevent dementia (Ude et al., 2013). It has also been claimed to have beneficial effects on atherosclerosis, vertigo, and tinnitus, visual acuity, various neurological and psychological disorders (Zhou et al., 2004). However, data on the pharmacokinetics and bioavailability of EGb-761 extract, especially related to the central nervous system, are relatively rare (Ude et al., 2013). In some studies, the components of Ginkgo biloba (terpenoids, flavonoids) are pharmacokinetically characterized in plasma and the brain. With oral administration, EGb-761 significantly crosses the

blood-brain barrier and enters the central nervous system of rats (Ude et al., 2013).

In Germany, EGb-761 is currently officially approved for dementia (Zhou et al., 2004). In the United States, it is commonly used for dementia and Alzheimer's disease (Dziwenka & Coppock, 2016), but multicenter studies for its use in dementia are ongoing (Zhou et al., 2004). In addition, in vitro pharmacological research has also hypothesized that the ingredients in Ginkgo biloba are protective against neuronal degeneration caused by ischemic events (Klein et al., 2003; Mdzinarishvili et al., 2007).

Figure 1: Uses of EGb 761 in neuropsychiatric disorders



2.1 Effects of Egb-761 Extract in the Central Nervous System

In various experimental models, the effects of EGb-761 extract on the central nervous system and stress, anxiety, depression, learning, and memory, were evaluated (figure 1). There is little information about EGb-761 extract's impact on psychiatric disorders (Depression, anxiety, schizophrenia). Most clinical research evaluates EGb-761 extract on psychiatric symptoms of patients with dementia.

During the last decades, the extract from the leaves of Ginkgo biloba has become one of the most commonly used herbal medicine for dementia (DeFeudis & Drieu, 2000; Yuan et al., 2017). The EGb-761 extract is used increasingly worldwide and is recommended to treat geriatric memory disorders, including vascular and neurodegenerative dementia (Abdel-Kader et al., 2007). EGb-761 extract's effectiveness in treating mild to moderate dementia of different etiologies has been repeatedly shown in various clinical trials, but contradictory data has also been published (LeBars et al., 1997; Napryeyenko & Borzenko, 2007).

To date, no exact ideal drug exists to treat or hinder the progression of dementia. Cholinesterase inhibitors (rivastigmine, donepezil, or galantamine), N-methyl-D-aspartate receptor antagonist (memantine), nonsteroidal anti-inflammatory drugs, and nootropic agent (piracetam) are partially effective in dementia and the improvement of symptoms (e.g., reducing memory loss and confusion). However, many of these drugs have serious side effects, including gastrointestinal symptoms such as nausea, vomiting, and appetite loss. Therefore, alternative therapies are often favored by dementia patients (Yuan et al., 2017).

In international guidelines for dementia management, EGb-761 extract has been approved and marketed in many countries as a supplement food product for phytotherapy purposes (Lang et al., 2013). However, FDA has not approved the medical use based on the inconsistency and inadequacy of present evidence (Yuan et al., 2017).

2.1.1 Antioxidant Effects of EGb-761 Extract

With aging, mitochondrial membrane changes potentially increase oxidative stress due to mitochondrial activity, and decreased respiratory chain activity is observed (Abdel-Kader et al., 2007). Furthermore, an increase in oxidative stress is essential in the pathophysiology of diseases, including dementia, psychiatric disorders, and Alzheimer's (Eckert et al., 2005; Abdel-Kader et al., 2007; Leuner et al., 2007; Mancuso et al., 2007).

On the other hand, Flavonoids are well-known antioxidants and can protect cell components from oxidative stress so that they can hinder the risk of oxidative stress-related neurodegeneration (Maclennan et al., 2002). Previous research has shown that EGb-761's multifunctional antioxidant properties may protect against oxidative stress (Maitra et al., 1995). Marcocci et al. (1994) employed the 7'-dichlorofluoresin (DCFH) method to examine the effects of EGb-761 on hydrogen peroxide levels in cerebellar neurons. Intracellular hydrogen peroxide oxidizes DCFH to dichlorofluoresin (DCF), which is a highly fluorescent compound. EGb-761 decreases the density of DCF and has similar effects in Ca^{+2}-charged neurons.

Flavonoids are thought to have potential power in managing Alzheimer's disease. In Alzheimer's, neurofibrillary tangles are formed due to amyloid β-derived plaques and hyperphosphorylated tau proteins. Flavonoids have been claimed in some studies to hinder the formation of amyloid β-induced plaques. For example, Ono et al. (2003), and Jiménez-Aliaga et al. (2011) showed that flavonoids myricetin and rutin inhibit the formation and aggregation of amyloid β fibrils at effective concentrations.

2.1.2 Effects on Neurotransmission Modulation

Neurotransmitters serotonin, dopamine, noradrenaline, glutamate, and GABA are subjected to changes in psychiatric disorders. For example, disorders such as depression and anxiety, occur due to changes in serotonin, dopamine, and noradrenaline neurotransmission (Ressler & Nemeroff, 2000). On the other hand, a change in dopaminergic neurotransmission is associated with the pathophysiology of schizophrenia (van Os & Kapur, 2009).

There is evidence that EGb-761 extract can balance monoamine activity involved in mood and anxiety disorders (Fehske et al., 2009). Long-term application of EGb-761 extract to aged rats has been shown to increase serotonin levels and 5-Hydroxyindoleacetic acid, which is associated with spatial memory (Blecharz-Klin et al., 2009). In contrast, another study showed that EGb-761extract (14 days/once a day) administration to rats did not affect serotonin levels but increased extracellular dopamine and noradrenaline levels in the prefrontal cortex (Yoshitake et al., 2010). In addition, Fehske et al. (2009) showed that EGb-761 extract could inhibit monoamine oxidase (MAO). Furthermore, in rats, EGb-761 extract has been shown in vivo to increase noradrenergic, dopaminergic, and cholinergic neurotransmission (Kehr et al., 2012).

One of the significant pathological changes in Alzheimer's disease is the degeneration of cholinergic neurons in the cerebral cortex and hippocampus. The magnitude of neurodegeneration is associated with the severity of cognitive changes in patients with Alzheimer's disease (Collerton, 1986). By regulating cholinergic nerve conduction (Montes et al., 2015) EGb-761 can even reverse changes in cholinergic neurons. In a rat study, EGb-761 extract was shown to prevent memory impairment when given 100 mg/kg with a cerebroventricular infusion (Krištofiková & Klaschka, 1997).

2.1.3 Effects on Hormones on the Hypothalamo-Pituitary-Adrenal HPA) Axis

Psychological disorders are caused by changes in hormonal levels and changes in neurotransmitter systems. Depression and anxiety have been associated with the hormonal fluctuations in the hypothalamic-pituitary-adrenal (HPA) system during stress (McEwen, 2007). EGb-761 has been shown to regulate hormone levels in animal models and humans, which are necessary for normal brain function. EGb-761, due to its anti-stress effect, can also suppress changes in corticosteroid levels (Rapin et al., 1994).

Continuous administration of ginkgolide B, the active ingredient of EGb-761, to isolated rats has been shown to inhibit the increase in stress-

induced corticosteroid secretion by affecting peripheral benzodiazepine receptors (Amri et al., 1996; Amri et al., 1997). Also, EGb-761 and one of its components, Ginkgolid B's effects on the biosynthesis and secretion of the pituitary-adrenal axis of neurohormones that regulate hypothalamic corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) were investigated. Oral EGb-761 extract was given to rats for two weeks, and it was found that corticosteroid secretion and the increase in CRH and AVP gene expression were inhibited (Marcilhac et al., 1998). Also, there is evidence that EGb-761 extract has an inhibitive effect on corticosteroid production in response to stress stimuli in healthy people (Jezova et al., 2002). However, administration of EGb-761 extract to healthy volunteers did not affect primary androgenic steroid hormone (Markowitz et al., 2005). Furthermore, EGb-761 extract has been found to increase testosterone production in vitro, reducing prolactin production by Leydig cells, which increases sexual behavior (Yeh et al., 2008). Changes in sexual behavior are often seen in psychiatric disorders.

2.1.4 Effects on Neurotrophic Factors

Neurotrophic factors are essential for maintaining neuronal functions (Masi & Brovedani, 2011). Changes in levels or signals of neurotrophic factors are associated with pathophysiology in developing psychiatric disorders (Autry & Monteggia, 2012). Preclinical studies have shown that an increase in brain-derived neurotrophic factor (BDNF) is involved in the neuroprotective effects of EGb-761 (Montes et al., 2015). The up-regulation of cyclic AMP-response element-binding protein (CREB) activity is associated with the increase in BDNF and EGb-761 (Hou et al., 2010; Autry & Monteggia, 2012). One of the significant mechanisms of neuroplasticity is the activation of the transcription factor CREB and subsequent induction of genes encoding neurotrophic factors. These mechanisms are disrupted in mood disorders (Pittenger & Duman, 2008).

It has been shown that in tardive dyskinesia (TD), symptoms improved with EGb-761 therapy and increased BDNF levels compared to placebo therapy in schizophrenia patients (Zhang et al., 2012).

2.1.5. Cerebral Ischemia-Protection Against Ischemia-Reperfusion Damage

In an experimental animal study, antioxidant and vasodilator properties of EGb-761 provided neuroprotection by reducing acute cerebral ischemia-reperfusion (IR) damage and the volume of cerebral infarction (Chandrasekaran et al., 2002; Eckert et al., 2003). Eckert et al. (2003) showed that reducing free radical formation and apoptosis EGb-761 inhibits the mitochondrial electron transport chain. Pre-treatment with EGb-761 prevents the phosphorylation of astrocytes from decreasing

during ischemic damage and regulating calcium, preventing damage and apoptosis of nerve cells during ischemia (Koh, 2012; Sung et al., 2012). EGb-761 has the effect of preventing ischemia and protecting neurons in chronic cerebral ischemia (Tian et al., 2017). Intragastric EGb-761 was given to atherosclerotic rats for eight weeks (100 mg/kg/day), resulting in reduced inflammation (IL-1β and TNF-α) and down-regulation in IL-10 and interleukin-10 receptors in the brain (Jiao et al. 2005).

3. CLINICAL USE IN CEREBROVASCULAR ISCHEMIC DISEASES

The EGb-761 extract is widely used to treat acute ischemic stroke in China and Europe. Although there are animal studies on the therapeutic potential, very few clinical studies investigate EGb-761 extract's effect on acute ischemic stroke (Hong et al., 2013; Oskouei et al., 2013). Oskouei et al. (2013) demonstrated that administration of EGb-761 to 102 patients with acute ischemia significantly lowered the National Health Stroke Scale (NIHSS) and reported that the EGb-761 extract has a positive effect in terms of functionality. Further randomized controlled trials are needed to elucidate EGb-761 extract's efficacy against stroke (Tian et al., 2017).

4. EGB-761 EXTRACT AND STRESS, DEPRESSION, AND ANXIETY

Stress, anxiety, and depression are associated with biological, cognitive, behavioral, and psychological changes defined as negative emotional experiences and are accompanied by high rates of psychiatric diseases (Saki et al., 2014).

Anxiety is the activation of emotional stimulation, which involves a sense of fear or worry. Although there are common pathophysiological mechanisms of anxiety and depression, it has diagnostically different symptoms. Therefore, anxiety-related pathogenic mechanisms include changes to secondary messenger systems, stress-induced HPA axis, and neurotrophic factors, as well as various neurotransmitters (monoamines) (Markou & Cryan, 2012).

Several biological factors are known to play a role in the complex pathophysiology of depression (Belmaker & Agam, 2008). The pathophysiology of depression is mainly associated with dysfunction of serotonergic neurotransmission, disruption of the production of secondary messengers, systems such as G proteins, or cyclic AMP (Ressler & Nemeroff, 2000; Hindmarch, 2001). However, excessive cortisol and CRH (Plotsky et al., 1998; Antonijevic, 2006) have been found to play a role in neuroendocrinological abnormalities such as the HPA axis (Herbert, 2013). In addition, a decrease in neurotrophic factors such as BDNF is associated

with decreased neurogenesis (Lee & Kim, 2010). Also, steroidal changes and changes in abnormal circadian rhythm are reported (Plotsky et al., 1998; Ressler & Nemeroff, 2000; Hindmarch, 2001; Raison et al., 2006; Bódizs et al., 2010).

Monoamine oxidase inhibitors (MAOI), serotonin-norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants are used in the treatment of depression. In treating anxiety disorders, anxiolytic antidepressants with anxiolytic properties and benzodiazepines are commonly used (Bystritsky et al., 2013). However, these drugs have undesirable effects, such as problems with the gastrointestinal tract, changes in sleep, weight, sexual behavior, and the risk of addiction (Bystritsky et al., 2013).

The EGb-761 extract is used for depression, anxiety, and stress disorders. Rapin et al. (1994) reported that stress (auditory perturbation) increased the number of learning errors in rats. In addition, the increased plasma concentrations of epinephrine, norepinephrine, and corticosteroids during stress were associated with behavioral disorders observed in the learning task. The EGb-761 extract inhibited unwanted effects of auditory perturbations and increased plasma hormones (Rapin et al., 1994).

Another study found that prolonged use of EGb-761 extract in rats caused a decrease in corticosteroid secretion. Marcilhac et al. (1998) found that plasma concentrations of CRH, adrenocorticotropic hormone (ACTH), and corticosteroids were significantly elevated in experimental animals under intense surgical stress, but this stress was significantly reduced in animals treated with EGb-761. Furthermore, EGb-761 improves learning and memory functions in animals exposed to stress (Pardon et al., 2004; Walesiuk et al., 2005). EGb-761 extract regulates some cognitive functions, especially decision-making in stressed mice (Pardon et al., 2004). In Ward et al.'s (2002) study, laboratory mice treated with EGb-761 showed less stress and less anxiety response than untreated mice.

There is evidence that EGb-761 extract has beneficial effects on patients' stress, depression, and anxiety. In one clinical trial (Woelk et al., 2007), patients with a generalized anxiety disorder and patients with adjustment disorder with anxious mood were randomized to receive either EGb-761 or a placebo. Hamilton Rating Scale (HAMA) was used to assess anxiety; thus, it was found that there was a significant decrease in anxiety parameters in both groups (high and low doses of EGb -761). It was also demonstrated that anxiety decreased more in the group taking high doses of EGb-761 extract than in the placebo group or the low-dose group. The study also showed that the anxiolytic effect of EGb-761 extract increased in a dose-dependent manner similar to those reported for benzodiazepines

(Woelk et al., 2007). The EGb-761 extract reduced stress-induced blood pressure in healthy young volunteers exposed to stressful stimuli (Jezova et al., 2002).

Stress and anxiety have also been found to alter the hormonal changes in the HPA system (McEwen, 2007). EGb-761 resulted in a more significant decrease in salivary secretion due to increased corticosteroid stress in male subjects than in the placebo group. Thus, it is suggested that EGb-761 has regulatory effects on stress-induced activation of the HPA axis (Jezova et al., 2002).

5. ADVERSE EFFECTS OF EGb-761 EXTRACT:

The most frequently reported adverse effects of EGb-761 are: gastrointestinal disorders (2.6%), nausea, headache (0.9%), sleep disturbances and dizziness (0.4%), and skin manifestations (0.3%) (Lacomblez et al., 1990; Letzel et al., 1996; Juretzek et al., 2002). Kleijnen & Knipschild (1992) reviewed the clinical safety of EGb-761. They demonstrated that EGb-761 did not cause severe side effects when administered at doses ranging from 120-160 mg for 4 to 6 weeks. Gavrilova et al. (2014) administered 240 mg of EGb-761 extract daily for 24 weeks in a double-blind, randomized, multicenter clinical trial and showed that the rate of non-severe side effects was not different from the side effects among the placebo group. Four studies identified side effects such as gastrointestinal disorders and bitter taste (Yang B & YM., 2003; Chen et al., 2004; Zhang CX & JQ., 2007; Lv Y & WY., 2009). They could not find a significant difference between the groups and showed that none of the side effects were severe and disappeared independently.

There are reports concerning the increased risk of bleeding with Ginkgo biloba extract (Bent et al., 2005). However, the reports were generally associated with different extracts from EGb-761 (Montes et al., 2015). For example, a case report noted a subdural hematoma in a 72-year-old patient who received EGb-761 extract (Gilbert, 1997). In another case, a 38-year-old woman who took thiamine and Ginkgo biloba extract for the last four years was found to have had a cerebral hemorrhage (Pedroso et al., 2011). Another report was a 70-year-old man who encountered spontaneous bleeding in the iris (hyphema) one week after he started taking another natural Ginkgo biloba supplement called Ginkoba. Moreover, the patient was also using aspirin. As a result, Ginkoba was stopped, but the patient continued to use aspirin, and no recurrent bleeding was reported after three months of follow-up (Rosenblatt & Mindel, 1997). Therefore, it has been suggested that the combined use of Gingko Biloba extract and aspirin may cause bleeding (Rosenblatt and Mindel, 1997). Reports which link Ginkgo biloba with increased bleeding are mainly case reports and

different extracts of EGb-761, as shown in the above examples (Montes et al., 2015). Therefore, it should be stated that each extract has different properties. Although these case reports concluded a relationship between Ginkgo biloba treatment and bleeding, more data is needed to reach a definite conclusion (Bent et al., 2005).

Also, information from specific EGb-761 studies is controversial. For example, in a placebo-controlled, double-blind, randomized trial, healthy volunteers were given three different doses of EGb-761 extract for 14 days, resulting in no changes in platelet function or coagulation factors (Bal Dit Sollier et al., 2003). However, in another similar study, healthy volunteers were given an extract of EGb-761 for seven days, and as a result, there was no evidence that blood coagulation and platelet aggregation decreased (Köhler et al., 2004).

More studies are needed to resolve these arguments. However, it is best suggested that especially susceptible patients using Ginkgo biloba extracts should be aware of the possible risk of bleeding (Bent et al., 2005).

Ang-Lee et al. (2001) reported that in 22% to 32% of patients who applied preoperatively using herbal medicines, EGb-761 extract ranked eighth among the most frequently used. There are isolated case reports on adverse drug-drug interactions between Ginkgo biloba and conventional drugs (Skogh, 1998; Vale, 1998; Fong & Kinnear, 2003). Ang-Lee et al. (2001) suggested that EGb-761 extract should be discontinued 36 hours before surgery, potentially increasing the risk of bleeding in EGb-761 users. Sierpina et al. (2003) suggested that the EGb-761 extract has the risk of inhibition of platelet activation with possible bleeding risk when taken with other antiplatelet drugs.

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CHAPTER 13

RADIONUCLIDE AND CHEMICAL PRECURSORS FOR RADIOLABELLING OF CARRİER MOLECULES WİTH THE GALLIUM-68

Ayşe UĞUR[1]

1 (PhD).(Pamukkale University, Education and Research Hospital, Department of Nuclear Medicine) E-mail:ayseugur@pau.edu.tr

Gallium-68 (^{68}Ga) is obtained by elution from generator a long-lived Germanium-68 (^{68}Ge) radionuclide produced from a reactor or by a cyclotron. In cyclotron production, ^{68}Ge (half-life of 271 days) is produced from a stable isotope ^{69}Ga. ^{68}Ge is then immobilized in a filler filled column where it decomposes to ^{68}Ga (68 min half-life). (Kumar V, 2013). 68Ge/68Ga generators must be licensed and placed on the market with marketing authorization. These permits are also required for module kits or disposable kits and radionuclide precursors. Therefore, ^{68}Ga radiopharmaceuticals labeled in a cGMP-compliant, well-equipped laboratory cannot be radiopharmaceutical unless legally authorized by one of the required starting materials, i.e., one of the radionuclide precursors (Neels, 2019).

Medicines within the scope of the European Union Directive 2001/83 defines radiopharmaceuticals as "any ready-to-use medicinal product containing one or more radionuclides for a medical purpose" (European Union. , 2014: L158/1–76). In the pharmacopoeia published by the World Health Organization in 2008, radiopharmaceutical products were examined in four stages.

1. Radiopharmaceutical preparation
2. Radionuclide generator
3. Radiopharmaceutical precursor
4. Kit for radiopharmaceutical preparation

The Pharmacopeia defined the radiopharmaceutical precursor in step 3 as follows; "A radionuclide ultimately produced for radiolabelling with a radiopharmaceutical preparation". The complexity of the definitions here and in other regulations has created difficulties in understanding the definition of radiopharmaceutical precursor (Ph. Eur., 2020).

As is known in Nuclear Medicine, different radionuclides (such as ^{18}F, ^{131}I, ^{177}Lu, ^{68}Ga) are studied. In this publication, we will try to explain "radiopharmaceutical precursors" in the preparation of radiopharmaceuticals labeled with ^{68}Ga radionuclide used for diagnostic purposes in Nuclear Medicine. The purpose of the review is not to examine the applications and all properties of ^{68}Ga radiometal, but to give the reader a basic idea of the precursors in the preparation of ^{68}Ga radiopharmaceuticals and the radiochemical and chemical properties of these precursors under optimized conditions.

1. $[^{68}Ga]^{68}GaCl_3$ chloride precursor for radiolabeling

Chemical precursors are defined as "starting chemicals used in a chemical synthesis". Precursors in radiopharmaceuticals are radioactive

and non-radioactive substances that react chemically for combination with a radionuclide (Ph.Eur., 2020). Since these clinically used radiopharmaceutical precursors cannot be administered directly to the patient, their use has been determined by binding to a suitable pharmaceutical vector in kit form (Ph.Eur., 2020). Therefore, in radiopharmaceuticals in clinical use in Nuclear Medicine, the precursor can be defined as both a radionuclide precursor and a chemical precursor. In the use of a new radiopharmaceutical precursor in applications, it is expected to determine quality control tests and serve the purpose of use. And it is important to determine the chemical contamination of the material to be used in the production of each precursor and to confirm its purity. After all necessary tests, additional tests should be performed if necessary according to the identity of the radionuclide.

In the latest edition of the European Pharmacopoeia (Ph. Eur., 2020), several chapters have been published on the quality control of drugs. Pharm Eur. There are also special monographs on radiopharmaceuticals. Although there are defined monographs on chemical precursors, there is no defined monograph on radionuclides or radionuclide precursors. The general monograph "Radiopharmaceutical preparations" (Ph. Eur., 2020) is considered for the radionuclide precursors that we use in the clinic today. This monograph contains definitions for the radiochemical purity test of the radionuclide, as well as for sterility and bacterial endotoxin testing.

Quality control requirements, radionuclide purity and specific activity values of ^{68}Gallium radiopharmaceuticals used for diagnosis in Nuclear Medicine vary according to the material obtained. That's why Ph.Eur. There is no general monograph that covers all radionuclide precursors. Monographs of radionuclide precursors such as Fluor-18, Iodine-123 and -131 or Indium-111 are defined under the heading of radiolabeling in the monographs under the responsibility of the European Medicines Quality Directorate (EDQM), an organ of the Council of Europe. In 2020, two new monographs were added, ^{68}Ga-chloride solution (Monograph: 2464 , 2020) for radiolabeling and ^{68}Ga-chloride solution (Monograph:3109., 2020) solution for radiolabeling. Acceptance criteria for radiolabeling defined ^{68}Ga-chloride solution are shown in table 1.

Table 1. *Acceptance criteria for radiolabeling defined ^{68}Ga-chloride precursor (Monograph: 2464 , 2020)*

^{68}Ga-chloride precursor for radiolabelling (Monograph;2464)	
pH	Max. 2
Iron(III)	Max. 10 µg/GBq
Zinc(II)	Max. 10 µg/GBq

Radionuclidic purity	- The amount of ^{68}Ga should be a minimum of 99.9 percent of the total radioactivity in the elution. - Photons with energies of 0.511 MeV, 1.077 MeV, 1.022 MeV and 1.883 MeV do not represent more than 0.1 percent of the total radioactivity. - The amount of ^{68}Ge should not be more than 0.001 percent of the total radioactivity.
Radiochemical purity	The amount of [^{68}Ga]gallium(III) ion must be at least 95 percent of the total radioactivity.
Bacterial endotoxins	Bacterial endotoxin should be less than 175 IU/V for a single patient dose.

When the table is examined, the criterion that the $^{68}GaCl_3$ precursor should not exceed pH:2 is generally provided. The $^{68}GaCl_3$ precursor obtained from $^{68}Ge/^{68}Ga$ generators is eluted with a strong acid. When radiochemical impurities are examination, $^{68}Ga(III)$ ion content should be 95% of the total activity and other forms of $^{68}GaCl_3$ ion should not exceed 5%. If this ratio is higher, it causes non-target organ involvement and accumulation in unwanted chemical form. In this case, ^{68}Ga used for diagnostic purposes does not serve the desired purpose. The metallic pollution is the most important criterion in the table. Differences in generator profiles due to production processes cause contaminations in the radionuclide precursor (Uğur A, 2021)

The effect of metal ions on the radiolabeling reaction of the ^{68}Ga isotope has been studied in many studies (publication).The metal ions that interfere most with ^{68}Ga are Cu^{2+}, Fe^{3+}, Ga^{3+} and Zn^{2+}. Ph.Eur. limits the contamination level of Zn^{2+} and Fe^{3+} metal ions to 10 µg/GBq for ^{68}Ga produced by cyclotron (Pharmeuropa 30.4.).Some of the generators available in the market use a cartridge (like PSH^+) system to reduce this pollution.

If the radiometal produced by the cyclotron is supplied by one manufacturer and the marking is carried out in another laboratory, the metal content of the elution produced from the generator should be tested. Complex formation may originate from the column material or may occur later on. There may be many metal sources in the laboratory environment and trace metal pollution can easily enter the radiometal production process at various pointsUnfiltered laboratory environment may contain certain amounts of rust and metal dust, and syringes also cause traces of metal contamination (EPA's (OW)., 1997) (Forgács, 2022). In-house methods may be preferred for determination of metal content. The concentration of metallic impurities in the generator elution can be determined after decay of radioactivity using ICP-OES or ICP-MS techniques. Although production differences prevent a standard quality control, each radionuclide precursor should be evaluated based on its own production certificate (Uğur A, 2021).

Finally, the $^{68}Ge/^{68}Ga$ generator used in the production of ^{68}Ga-chloride precursor is the main element that fulfills all the criteria mentioned above. Therefore, the following features should be considered when choosing a $^{68}Ge/^{68}Ga$ generator:

- Volume elution
- Germanium-68 breakthrough
- Elution properties consistent with the half-life of the generator
- Metal ion contamination due to column material
- High radionuclide yield
- Compatibility with licensed radiopharmaceuticals (Burke, 2020).

2. Chelator-peptide bioconjugates for radiopharmaceuticals

Radiopharmaceuticals labeled with peptides and chelator-bioconjugates have a critical clinical impact in the diagnosis and treatment of many types of cancer. Peptides are a class of compounds that are gaining popularity in the theranostic application of many cancer diseases (Thundimadathil, 2012), (Jackson, 2020). These chemical precursors can be small organic molecules or high molecular weight biomolecules. Receptor-binding small molecule peptides are currently the preferred imaging agents for use in receptor-targeted imaging. The reasons can be listed as follows; small size, ease of labeling, enabling the use of different radio-labeling techniques, easy binding with chelates, receptor specificity with high affinity, high penetration into tumor tissue.

The solubility, structure and function of peptides are characteristic of amino acid composition and sequence (Okarvi, 2004). Peptide-based radiopharmaceuticals are expected to have a high degree of stability as well as renal excretion. Therefore, the developed radiopharmaceutical should be hydrophilic [meltem hoca tez]. Radiopharmaceuticals based on lipophilic peptides are excreted from the liver-biliary tract. Lipophilic radiopeptides show high background activity in the abdomen, masking the tumors there. This situation limits effective diagnosis and treatment. The rate and route of excretion of peptides from the body can be adjusted by adding specific hydrophilic or lipophilic amino acid residues to the peptide chain. In addition, more stable hydrophilic peptides are obtained by adding water-soluble polyethylene glycol (PEG) derivatives (pegylation), which are non-toxic and non-immunogenic to the peptides (Gotthardt D, 2006).

A linker is included between the peptide molecule and the chelating moiety to prevent the radiopharmaceutical from mixing with the binding site. For this before, the types of receptors specific to the tumor to be diagnosed or treated and the rates of their presence in the tumor are

determined. Then, the determination of the endogenous peptide specific to the specific receptor, which is intensely present in the relevant tissue, is performed. Synthetic analogues are synthesized based on the detected endogenous peptide. Appropriate chelates are attached to the synthesized peptides for use in radiolabeling processes (Thomas Ebenhan, 2014).

Coordination of gallium is utilized in labeling peptides with ^{68}Ga radionuclides. The chelate chemistry of gallium is dominated by chelates containing oxygen and nitrogen donor atoms (Okarvi, 2004). Various chelating systems have been developed for the radiolabelling of bioactive molecules with gallium [such as NOTA and DOTA].

Radioligands used in radiopharmaceutical labeling mimic iron(III) in vivo due to their chemical similarity (especially ^{68}Ga). Transferrin (iron transport protein) has a high binding constant (logK = 20.3) for gallium(III), which promotes its uptake in the liver and lungs (Scott, 2020), (Philipp S., 2016). This encourages the use of hexagonal chelators and macrocyclics as chelators. Peptide/chelate precursors used in radiolabelling are expected to have certain properties. The most important of them are; Such as pH, temperature, time, metal ion selectivity. Because the radiolabeled tracer takes time to separate from the starting material and works in practice, any unlabeled precursor will survive in the composition of the radiopharmaceutical and compete with the radiolabelled derivative to reduce or block binding to the targeted proteins.

If the chelator used in the labeling cannot distinguish ^{68}Ga from the generator or from outside metal cations (especially zinc(II)), radio labeling efficiency will decrease and more precursor, time or temperature will have to be used. This will create process complexity and reduce the targeted service towards the target.

The biggest challenge in radiolabeling with ^{68}Ga radionuclide is the hydroxide formation of ^{68}Ga. At low pH values (<3), $[Ga(H_2O)_6]^{3+}$ form will be formed in the form of ionic gallium(III) or hexahydrate, and at this pH most chelators will become protonated and unusable. If the pH is above 7, the colloidal form $[Ga(OH)_4]^-$ is formed. In ^{68}Ga radiochemistry, the pH:3-7 range should be chosen to meet the appropriate labeling and chelator requirements. In these pH ranges $[Ga(OH)]^{2+}$, $[Ga(OH)^{2+}$ and $Ga(OH)_3$) species are found [24–26]. In radiolabelling with the commonly used chelator, pH 4-5 is ideal, and as the temperature rises, the formation of low stability $Ga(OH)_3$ increases (Burke, 2020).

Some of the chelators commonly used in clinical studies are shown in figure 1 and their properties are tried to be explained below.

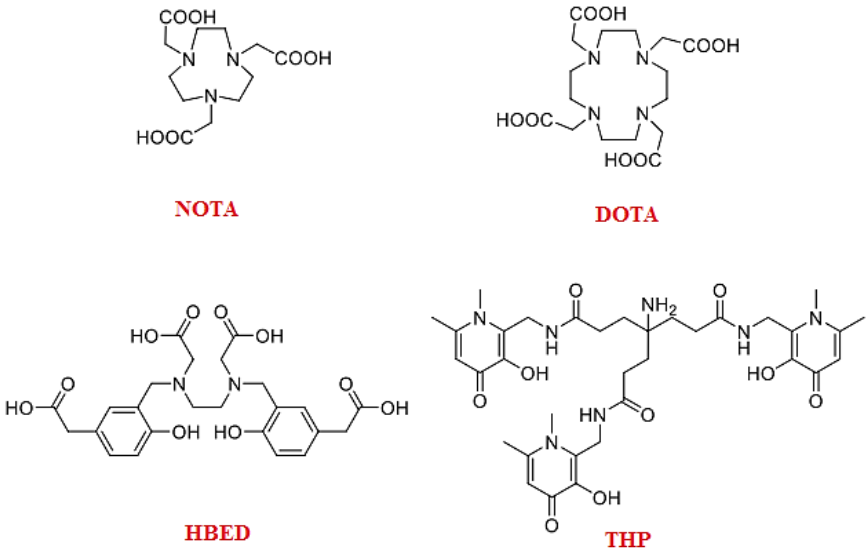

Figure 1. Chemical structures of common chelators used in ^{68}Ga radiolabeling.

• ***1,4,7-Triazacyclononane-N,N",N"-triacetic acid (NOTA)*** (figure 1) is a macrocyclic chelator made with acetate donors attached to secondary amines. NOTA binds to gallium(III) via an N_3O_3 coordination sphere on which the metal ion sits on the N_3 plane of the macrocycle Radiolabeling of NOTA with ^{68}Ga can be performed at room temperature to form complexes with high stability in vivo. The NOTA reaction with ^{68}Ga is readily labeled at a slightly acidic pH (4-5), with a radiolabeling time of about 10 minutes (Notni J, 2010).

• ***1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)*** (figure 1) is the most widely used ^{68}Ga chelator and can also be easily chelated with other metals (^{68}Ga, $^{64/67}$Cu, $^{44/47}$Sc, ^{111}In, ^{177}Lu, $^{86/90}$Y, ^{89}Zr and ^{225}Ac) in Nuclear Medicine (Price, 2014). Insertion of a metal into the central macrocyclic space or siting above the N_4 plane of the macrocycle by wrapping acetic acid around the hanging arms achieves complex formation. Since ^{68}Ga(III) ion is formed by N_4O_2 bonding with steric interaction in the backbone, it becomes complex with radiochemical reactions that require high temperature (Blower, 2019).

• ***N,N'-Bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED)*** (figure 1) is an acyclic chelator developed from ethylenediaminetetraacetic acid (EDTA) backbone. Its most common derivative is N,N'-bis-[2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine N,N'-diacetic acid (HBED-CC), and its acyclic structure allows it to complex even at room temperature (Eder M, 2008). The use of HBED-derived chelates in

the design of PSMA-11 has proven to be a chelator serving its intended purpose.

• ***Tris(hydroxypyridinone) (THP)*** (figure 1) is an acyclic chelator and is particularly ideal for gallium(III) coordination. THP can be used to radiolabel biomolecules at low chelator concentrations almost instantly at pH 6.5 at room temperature, makes its use ideal (Imberti C, 2019). Among these chelators, DOTA and HBED chelates are the most commonly used for ^{68}Ga. Since DOTA is not particularly selective for ^{68}Ga compared to other metal ions, the resulting molar activity may be low if the generator eluates are not pre-purified. DOTA has a disadvantage in labeling non-heat-sensitive biomolecules as it requires heat for efficient radiolabeling. While HBED does not require pre-purification and high temperature, its isomeric nature may pose a problem in binding kinetics. The chelators of NOTA and THP can be radiolabeled at low concentrations with ^{68}Ga at room temperature (Tsionou, 2017).

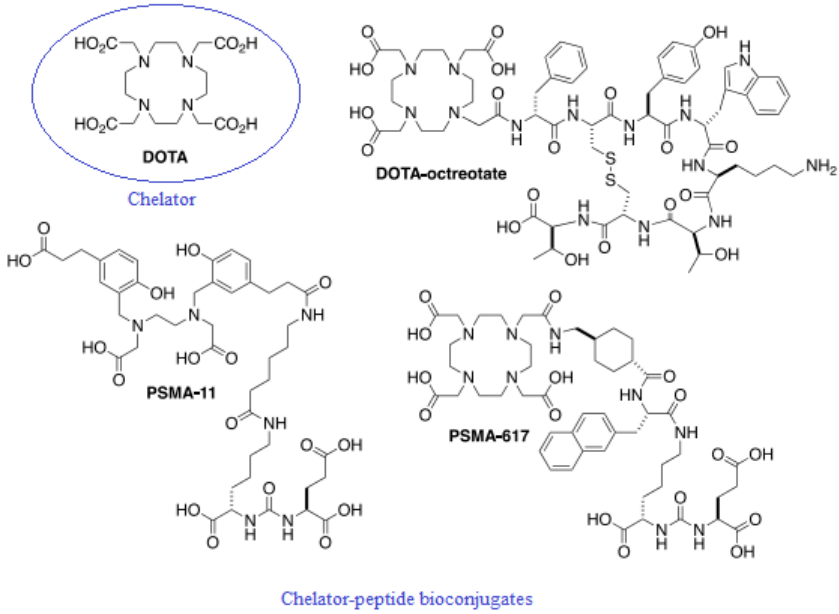

Figure 1. DOTA chelator and chelator-peptide bioconjugates commonly used to label ^{68}Ga-peptides

With the success of radionuclide labeled peptides in molecular imaging, PSMA-peptides have also taken their place in the clinic. DOTA conjugates add lipophilic "linker" groups between the chelating motif and the PSMA peptide, providing favorable hydrophobic interactions between the radiotracer and the PSMA receptor's hydrophobic binding "pocket" (Burke, 2020).

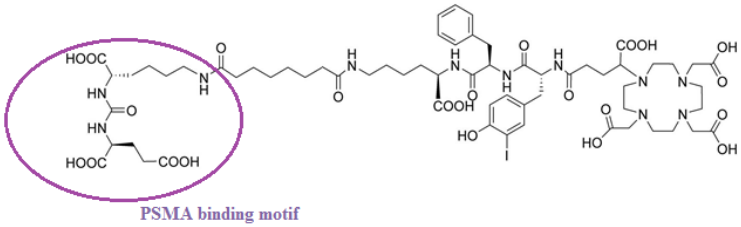

Figure 2. PSMA I&T chemical structure and binding motif

3. Chemical precursors for radiolabeling

In addition to these precursors, impurities in the peptide precursors of residual solvents need to be examined as well. The solvents used in the synthesis of pharmaceuticals are defined as organic volatile chemicals. Residual solvents should be removed as much as possible in the radiopharmaceutical composition to meet good manufacturing practices (GMP) or other quality-based requirements. Solvents cannot be completely eliminated during production. Certain solvents (Class 1) known to cause unacceptable toxicities in accordance with ICH guideline Q3C (R6) should not be used in the production of drug substances or drug products unless their use is mandatory (ICH guideline Q3C (R6), 2016). Some solvents associated with less severe toxicity (Class 2) should be limited to protect patients from potential side effects. Ideally, less toxic solvents (Class 3) should be used where practical. Residual solvents are determined using chromatographic techniques such as gas chromatography (GC) for the analytical determination of solvents. Solvent is used in chromatographic analysis of peptides (ICH guideline Q3C (R6), 2016). However, to the advantage of the SPPS and lyophilization process, the most frequently detected solvent is only acetonitrile, which is used as a component of the mobile phase in the final purification by preparative HPLC (Nussbaum, 2000).

4. Quality controls of radionuclide and chemical precursors

Radionuclidic purity is defined as the ratio of the desired radionuclide activity to the total radioactivity in a radiopharmaceutical. It is expressed as a percentage (Pijarowska-Kruszyna, 2021). Depending on the generator matrix, the $^{68}GaCl_3$ precursors can be heavily contaminated with inorganic and/or organic chemicals. Therefore, direct labeling procedures using generator eluate may fail or cause low efficiency (Eppard, 2017). Successful manufacturing and quality control processes must be completed to ensure that the final product radiopharmaceutical meets regulatory requirements regarding contaminants (Taratonenkova, 2019).

For a quality radiolabeling, a preliminary quality assessment of the

peptides should also be made by visual inspection of appearance/color and resolution. Metallic contamination of peptide precursors (Pt, Pd, Mo, Ni, Pb, Hg, Cd, Tl...) affects complex formation in radiolabeling. The presence of metals in the labeling of $^{68}GaCl_3$ precursor peptide precursors greatly reduces labeling efficiency through competitive chelation with gallium precursor. The metal impurity content in the peptide composition is limited to 0.01% (Aslani, 2014). Metal impurities in the peptide composition can be investigated using atomic absorption spectrometry (AAS), atomic emission spectrometry detection (ICP-AES) or mass spectrometry detection (ICP-MS) techniques using inductively coupled plasma.

The stability of the radiolabeled peptide is primarily studied in a buffer solution whose concentration is low enough to provide in vivo conditions (such as phosphate buffer, pH 7.4). If sufficient stability (<10% loss, after 6-24 hours of incubation at 37°C) can be achieved in aqueous solution, in vitro serum stability should be checked. The loss of activity in the serum may be due to the thermodynamic instability of the radiolabeled peptide, the formation of complexes with proteins (albumin, etc.) and the presence of peptidases. The method to be used in stability tests are molecules that are capable of illuminating all impurities that may occur, such as small ions or complexes, radiolabeled amino acids or peptide fragments or protein fragments. The most reliable analytical method for this type of analysis is radio-high performance liquid chromatography (R-HPLC) (Aloj, 2004), (Velikyan, 2015). An exemplary R-HPLC chromatogram is shown in fig 4.

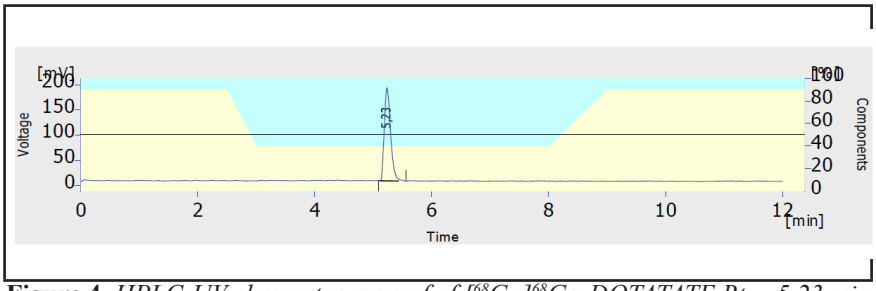

Figure 4. *HPLC-UV chromatograms of of [^{68}Ga]^{68}Ga-DOTATATE Rt = 5.23 min method: Mobile phase: 0,1% trifluoroacetic acid (TFA) in water (A) and 0,1% TFA in acetonitrile (B) gradient method 10-30% (B) in 10 min, Agilent C18 column, The injection volume 20 µL.*

In the absence of a specific monograph for the radiopharmaceutical to be prepared, analyzes can be performed using the appropriate analytical methods presented in table 2. For each test to be performed, the suitability of the use of the precursor radionuclide should also be checked (Pharmeuropa, 2014).

Table 2. *Analytical parameters and methods for a radiopharmaceutical without a defined monograph (Pharmeuropa, 2014)*

Test or parameter	Equipment or method
Characters, appearance	Visual inspection
Identity of radionuclide	Ionisation chamber (half-life), gamma-ray spectrometry
Radiochemical purity	Liquid chromatography, thin-layer chromatography
Chemical purity	Liquid chromatography, thin-layer chromatography, ultraviolet/visible absorption spectrophotometry
Residual solvents	Gas chromatography
Pharmaceutical or physiological parameters	pH, osmolality
Radionuclidic purity	Gamma-ray spectrometry
Specific radioactivity	Liquid chromatography, ionisation chamber
Microbiological parameters	Bacterial endotoxins, sterility

Sonuç

The section published in the European Pharmacopoeia on "Temporary preparation of radiopharmaceuticals" also mentions the use of radiochemical precursors for the preparation of radiopharmaceuticals. While GMP requirements are not required for cyclotron or reactor production, there is a definition that the purification and formulation of radionuclides should be considered (Decristoforo, 2017).

The radiopharmacist who prepares the licensed radiopharmaceutical is responsible for the preparation of this radiopharmaceutical and its quality after marking. Chemical precursors are usually obtained by synthesis (can also be of animal or human origin). It can be combined with other materials in the form of pre-made kits for radiolabeling procedures. They can be used as starting material in disposable kits or in cassettes mounted on the module. The quality requirements for chemical precursors are set out in the relevant monographs. In the absence of any monograph, the general monograph Substances for Pharmaceutical use (2034) is applied and a program for quality testing is implemented. It should be noted, however, that certain provisions of the general monograph on substances for pharmaceutical use (2034) do not apply to radiopharmaceutical components or chemical precursors. These provisions fall within the scope of the general monograph Radiopharmaceutical preparations (0125).

Since radiopharmaceuticals generally show their effects in different parts of the body (tissue) to which they are applied, it is desirable that

they have appropriate in vivo stability up to the region where they are expected to act. The quality control process is vital to ensure the safety and effectiveness of the radiolabeling procedure.The requirements for radiopharmaceuticals covered by the Directive are for radionuclide generators, kits and so-called radionuclide precursors. The definition of a radionuclide precursor includes practically all radionuclides and imposes high requirements for radionuclide manufacturers who aim to supply a radionuclide to a hospital or research facility for the preparation of a radiopharmaceutical, which has been discussed in detail recently.

There is no data on the effect of different conditions in optimization studies on the stability of the developed radiopharmaceuticals. This also prevents the stability of similar radiolabeled peptide analogues under development from being compared with each other. At the same time, these limitations raise the need for qualitative assessment of the suitability of radiopharmaceutical precursors to ensure the efficacy and safety of treatment. It is necessary to provide the standards for the production and quality control of these precursors by determining the specifications and acceptance criteria. Studies on the development of many new receptor-targeted radiopharmaceuticals for diagnosis and treatment in nuclear medicine applications are increasingly continuing. The Nuclear Medicine and Molecular Imaging Society (SNMMI) selected images with ^{68}Ga radioisotope as “Image of the Year” four times at its annual meetings between 2015-2020 and increased the interest in the ^{68}Ga radioisotope. After many studies on this radionuclide, he brought ^{68}Ga radionuclide from radiolabeling with manual-auto module to radiolabeling with disposable kit. The clinical future of the ^{68}Ga radioisotope lies in its becoming an imaging agent that will become widespread in global use, using a wide variety of radiopharmaceuticals produced with inexpensive and easy labeling techniques. With the development of new chelates in the future, it is likely that a fixed list of chelators will be used. The relationship between binders, chelator properties and peptide will be used to achieve optimal efficiency labeling under optimum conditions.

Anahtar Kelimeler: Radionuclides, radionuclide precursor, radiopharmaceutical precursors, peptides, European Pharmacopeia

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CHAPTER 14

SLEEP BRUXISM IN CHILDREN, ETIOLOGY AND TREATMENT APPROACH

Enes Mustafa Aşar[1], Büşra Muslu Dinç[2]

1 Selçuk University Faculty of Dentistry, Department of Pediatric Dentistry, Konya, Turkey, e-mail: enesmustafasar@gmail.com (Orcid: 0000-0003-3432-8584)

2 Selçuk University Faculty of Dentistry, Department of Pediatric Dentistry, Konya, Turkey, e-mail: dt.busramuslu@gmail.com (Orcid: 0000-0002-0230-5241)

Introduction

Bruxism is repetitive muscle activities that are of interest to various sciences such as dentistry, sleep medicine, neurology (Frank Lobbezoo et al., 2013). Although there are various dental problems in its etiology, the diagnosis and treatment process is difficult (Frank Lobbezoo, Van Der Zaag, Van Selms, Hamburger, & Naeije, 2008; Paesani, 2010). Bruxism may occur during sleep (indicated as sleep bruxism) or during wakefulness (indicates as awake bruxism) (Frank Lobbezoo et al., 2013). This can lead to various problems such as hypertrophy of masticatory muscles, headaches, tooth wear, periodontal diseases, joint disorders (Glares & Rao, 1977; Thompson, Blount, & Krumholz, 1994). While sleep bruxism (SB) occurs as a result of rhythmic or non-rhythmic chewing muscle activity during sleep, awake bruxism is characterized by repetitive tooth contact and protrusion of the mandible while the patient is awake (Frank Lobbezoo et al., 2018). There are many risk factors associated with bruxism. Bruxism is a common public health problem in childhood when growth and development continues (Guo et al., 2018). Despite this, there are still unresolved problems related to the etiology and clinical management of bruxism (Castroflorio et al., 2015). Recent study results suggest that SB may lead to primary headaches regulated by the central nervous system (Zieliński, Ginszt, Suwała, Szkutnik, & Majcher, 2019). At the same time, bruxism causes many sleep problems. Parasomnias, obstructive sleep apnea, restless legs syndrome, rapid eye movements are some of these problems (Oliveira, Bittencourt, Marcon, Destro, & Pereira, 2015).

Etiology of bruxism

As it has been known for years, the etiology of bruxism can be affected by many factors (Negoro et al., 1998). Factors such as temporomandibular joint disorders, hypopnea, high anxiety, malocclusion, and stress predispose to the emergence of bruxism (Claudia Restrepo, Gómez, & Manrique, 2009). Etiological factors create a change in dapamine neurotransmission and send a movement stimulus to the central nervous system. Teeth grinding and clenching may occur in response to this movement (F Lobbezoo, Soucy, Montplaisir, & Lavigne, 1996).

If we look at the etiology of bruxism from a pathophysiological point of view, the development of the masticatory neuromuscular system is held responsible, especially in young children (Patıroğlu, Didinen, & Tuğba, 2016). Apart from these, factors such as alcohol, smoking, trauma, diseases, medical interventions can also cause bruxism (Quintero et al., 2009).

Character and stress have an effect on the etiology of bruxism (Frank Lobbezoo, van der Zaag, & Naeije, 2006). In a study, it was reported that the anxiety of bruxism patients was also high (Kampe, Edman, Bader,

Tagdae, & Karlsson, 1997). In another study, an increase in catecholamine levels was observed due to emotional stress and it was shown that anxiety and stress have an effect on bruxism (Vanderas & Papagiannoulis, 2002).

Changes such as shifting of the tooth tubercles and inappropriate contacts were seen as the most common cause of bruxism. However, it has been shown in the following years that occlusal contacts do not cause bruxism (Quintero et al., 2009). In a study showing that bruxism is associated with respiratory problems, dental caries, and malocclusions, it was shown that there was no effect on quality of life (Antunes, Castilho, Marinho, Fraga, & Antunes, 2016). In a study conducted on twin children, it was shown that SB continues into adulthood (Carlsson, Egermark, & Magnusson, 2003). At the same time, it has been observed that any family member of patients with bruxism has a history of grinding in childhood (Lavigne, Khoury, Abe, Yamaguchi, & Raphael, 2008). In studies on the genetic effect of bruxism, the effect of genetic factors was found to be statistically significant (Wang, 2011; Zhu et al., 2009).

Diagnosis of sleep bruxism in children

According to the International Classification of Sleep Disorders, SB is a movement disorder seen during sleep (Medicine, 2005). It occurs as the body's response to stimuli during sleep. Bruxism is associated with an increase in heart rate and muscle tone that persists for 3-10 seconds, which can occur 8-15 times per hour in healthy individuals (Lavigne et al., 2008). SB may be associated with different sleep disorders such as waking up confused, sleepwalking, and talking during sleep (Beddis, Pemberton, & Davies, 2018). In SB, excessive increase in muscle activities is seen during sleep. People without SB may also have active chewing muscles during sleep, but this is much milder and the teeth are not in contact (Shochat et al., 2007). An increase in respiration was observed when SB was stimulated. Therefore, bruxism seen during sleep may be the body's response to increase the airway (Khoury et al., 2008). Usually, muscle activities begin with the suprahyoid muscles followed by the jaw opening muscles. The work of these muscles also extends the airway by positioning the mandible anteriorly and opens the airway (Lavigne et al., 2008).

Miyawaki et al. (2003) found that those with SB were more likely to have Gastro-esophageal reflux. They also observed that episodes of SB often occur during reflux. Additionally, those taking proton pump inhibitors had fewer episodes of bruxism during sleep (Miyawaki et al., 2003). Swallowing during sleep is more common following episodes of bruxism. This situation suggested that bruxism may be related to the stimulation of salivary flow during sleep (Lavigne et al., 2008). It has been found that swallowing increases due to increased muscle activities in

bruxism (Miyawaki et al., 2003).

Many methods can be used in the diagnosis of bruxism.

- Patient report and clinical interview
- Clinical examination
- Intraoral appliances
- Recording of muscle activity
- Electromyography (EMG)
- Polysomnography (PSG)

The paths to be followed in establishing the diagnosis of bruxism are shown in table 1 (Beddis et al., 2018). Direct association of masticatory muscles and temporomandibular joint pain with bruxism may lead to misdiagnosis. In many studies, it has been seen that joint and muscle pains are not caused by bruxism in diagnoses made using polysomnography (Raphael et al., 2012; Smith et al., 2009). In diagnoses made without the use of polysomnography clinically, the diagnosis of bruxism can be made more than it is. In addition, from the clinical observations suggesting bruxism in Table 1, it is very difficult to say that especially the tooth surface loss is caused by bruxism. There may be physiological abrasions in the mouth, erosions, abrasions caused by edible food and even bruxism-related abrasions from years ago. Therefore, wear alone cannot be an indicator of bruxism (Beddis et al., 2018).

Electromyography (EMG) electrically monitors and records muscle activity by connecting to the skin over the masseter and temporal muscles. However, we cannot detect teeth grinding with EMG. In addition, it cannot distinguish between different muscle activities such as chewing and swallowing (Lavigne, Rompre, & Montplaisir, 1996).

Polysomnography creates versatile recordings such as audio-visual recordings, electrocardiogram, electroencephalogram, EMG. In this way, it excludes conditions such as sleep disorders, muscle movements other than bruxism (Koyano, Tsukiyama, Ichiki, & Kuwata, 2008). Although complex and difficult to use, it is the gold standard for the evaluation of SB (Frank Lobbezoo et al., 2008).

Table 1: Auxiliary factors in the diagnosis of bruxism (Beddis et al., 2018)

Questions to ask when taking a history of bruxism	Are you notice that you grind your teeth while you sleep?
	Has anyone ever told you that you grind your teeth while you sleep?
	When you wake up, are your jaws clenched or do you stand out?
	Do you feel pain or stiffness in your jaw muscles when you wake up?
Questions for Bruxism Scale (van der Meulen, Lobbezoo, Aartman, & Naeije, 2006)	How often do you clench your teeth while sleeping?
	How often do you grind your teeth while sleeping?
	How often do you clench your teeth while awake?
	How often do you grind your teeth while awake?
Factors suggestive of bruxism on clinical examination	Masseteric hypertrophy
	Muscle tenderness on palpation
	Wear facets on occlusal surfaces or within the normal range of motion in eccentric jaw positions: termed “bruxofacet”
	Shiny spots on restorations
	Restoration or tooth fracture
	Tongue scalloping and ridging on the buccal mucosa (‘linea alba’)

There are many protocols for the diagnosis of bruxism. Among these, the most frequently used criteria are the criteria updated by the American Academy of Sleep Medicine in 2014 (American Academy of Sleep Medicine, 2014). Differently, SB-RDC is another diagnostic criterion with high sensitivity to detect SB (Lavigne et al., 2008).

Table 2: Diagnostic criteria of sleep bruxism

The American Academy of Sleep Medicine (American Academy of Sleep Medicine, 2014)	**A and B criteria must be ensured.** **A.** Frequent or regular hearing of teeth grinding sounds during sleep **B.** Presence of one or more of the following clinical findings 1- Abnormal tooth wear compatible with clenching during sleep 2- Temporary pain or fatigue in the jaw muscles in the morning; and/or temporal headache; and/or jaw locking upon waking in the morning due to teeth grinding
SB research diagnostic criteria (SB-RDC) (Lavigne et al., 2008)	Report of grinding noises by sleeping partner for at least 5 nights a week for the past 3-6 months One of: tooth wear into dentine with some loss of crown height; masseteric hyper trophy; positive PSG (at least 2 episodes of grinding noise per night, more than 4 SB episodes and more than 25 bruxism bursts per hour of sleep)

Treatment methods in bruxism

In a study investigating the effect of physical therapy in the treatment of bruxism, a significant reduction in teeth clenching and grinding rates was observed compared to the control group. Physical therapy is thought to be effective in the treatment of bruxism (Quintero et al., 2009).

There are many studies using occlusal splint applications in the treatment of bruxism (Carra, Huynh, El-Khatib, Remise, & Lavigne, 2013; de Oliveira et al., 2014; Jones, 1993; C. C. Restrepo, Medina, & Isabel, 2011). In 30 children who used occlusal splints, a decrease of more than 70% was recorded in line with the information given by the children and parents. In the same study, a significant reduction in headache and muscle pain was observed (de Oliveira et al., 2014). In another study, it was reported that headaches decreased and bruxism stopped after the use of an occlusal splint in a 5-year-old girl (Jones, 1993). It has been observed that the use of occlusal splints reduces bruxism in children aged 3 to 4 years with bruxism. However, the results in this study are statistically insignificant (C. C. Restrepo et al., 2011). Most of the studies were based on information provided by parents and children. In a different study, Rhythmic Masticatory Muscle Activity (RMMA) was evaluated quantitatively. A significant decrease was observed in RMMA values after 1 week with the use of splint positioning the mandible more anteriorly, and a decrease in SB was noted (Carra et al., 2013).

Studies in which orthodontic appliances are used in the treatment of bruxism have been published (Bellerive et al., 2015; Egermark

& Rönnerman, 1995; Giannasi et al., 2015). In a study using fixed orthodontic appliances, 50 children and adolescent patients reported that their headaches and bruxism decreased (Egermark & Rönnerman, 1995). In another study, they reported a significant reduction in patients' bruxism after rapid maxillary expansion (Giannasi et al., 2015). Again, a decrease in bruxism attacks was noted in a study in which visual examination was performed in the diagnosis of bruxism after maxillary expansion and quantitative examination was performed with RMMA (Bellerive et al., 2015).

It is aimed to reduce bruxism by using psychological treatment approaches, which are a different option. In a study conducted on 33 children in primary dentition using targeted muscle relaxation and reaction competence techniques, it was observed that bruxism was reduced statistically significantly with both techniques (CC Restrepo, Alvarez, Jaramillo, Velez, & Valencia, 2001).

Pharmacological methods have also been investigated in the treatment of SB. Many drugs such as flurazepam (15 mg/day), hidroksizin (25–50 mg/day ve 5–25 mg/day), trazodon (0,5 mg/kg/day), imipramin (25 mg/day), diazepam (2.5 ve 5 mg/day) have been tested in studies on this subject. All of these tested drugs reduced bruxism (Ghanizadeh, 2013; Ghanizadeh & Zare, 2013; Mostafavi, Jafari, Hoseini, Khademian, & Kelishadi, 2019; Reimão & Lefévre, 1982; Shakibaei, Gholamrezaei, & Heydarı, 2008). Muscle relaxants are also recommended in the treatment of bruxism (Winocur, Gavish, Voikovitch, Emodi-Perlman, & Eli, 2003). Although it has an advantage in treatment, side effects such as vomiting, nervousness, nausea, loss of appetite, confusion, drowsiness have been reported after pharmacological treatments (Chisini et al., 2020). Botolinum toxin, known as botox application, can reduce the frequency of bruxism. Long et al. (Long, Liao, Wang, Liao, & Lai, 2012) showed that botox application is as effective as occlusal splints. However, botox may carry the risk of causing osteopenic changes in the muscle attachment areas and condyle areas (Kün-Darbois, Libouban, & Chappard, 2015).

In the studies conducted in the following years, the use of alternative natural plants in the treatment of bruxism was tested. The use of medicinal extracts such as Melissa officinalis or Phytolacca decandra did not significantly contribute to the treatment of bruxism (Bortoletto et al., 2016; Silva, Primo, Mangabeira, Maia, & Fonseca-Gonçalves, 2017; Tavares-Silva et al., 2019). However, in a study where these two substances were used together, it was reported that tooth grinding decreased and did not recur for two years (Silva et al., 2017).

All these treatment methods, which have been shown to reduce

bruxism, have also improved different disorders seen during sleep (Chisini et al., 2020). After the use of flurazepam, a decrease in walking, speaking and night movements during sleep has been observed (Reimão & Lefévre, 1982). Appliances that position the mandible anteriorly reduce snoring up to 93% (Carra et al., 2013). Rapid maxillary expansion appliances have statistically significantly reduced problems such as night waking, snoring, and nighttime drooling (Giannasi et al., 2015).

In summary, many factors are effective in the etiology of bruxism. Although bruxism can be seen at any age, its prevalence is increasing day by day among children. Severe bruxism can have a detrimental effect on the mouth and teeth. For this reason, early diagnosis and taking precautions accordingly are important. PSG is the gold standard because it can make a versatile evaluation in its diagnosis. Dentists, in particular, are the first people who can make an oral diagnosis in terms of their field of work. For this reason, they should inform the child and family about bruxism and help with the necessary treatments. There are various applications and drugs that are effective in its treatment. More studies are needed on this subject in order to better understand and treat bruxism effectively.

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CHAPTER 15

BREAST PROBLEMS RELATED TO BREASTFEEDING AND ALTERNATIVE APPROACHES TO THE SOLUTIONS

Yasemin ÖZHÜNER[1] , Nebahat ÖZERDOĞAN[2]

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Introduction

Breastfeeding is a natural method that offers significant benefits for infant and maternal health, especially for proper nutrition of children and protection against disease (Lawrence, 2010). The World Health Organization (WHO) emphasizes the importance of breastfeeding and recommends that babies be fed only breast milk in the first six months of their lives (Karaçam & Sağlık, 2018). However, in the postpartum period, postpartum women may experience various problems during the breastfeeding process depending on the reasons arising from the baby and the mother. These problems cause the mother to not be able to breastfeed her baby effectively and to benefit sufficiently from breast milk. According to WHO, it has been observed that 98% of mothers breastfeed their babies, but then this rate drops to 35% in the first five months due to problems experienced during the breastfeeding process (Heller, Fullerton-Stone, & Murase, 2012; Agunbiade, & Ogunleye, 2012). The main reasons for these problems are: inadequate emptying of the breast, wrong positioning of the baby, not paying attention to hygiene, not breastfeeding regularly and frequently, late transition to breastfeeding after cesarean section, and incorrect application of breastfeeding techniques by mothers (Carlander, Edman, Christensson, Andolf, & Wiklund, 2010). According to Karacam et al. (2018), the most frequently reported breast-related problems that interrupt breastfeeding in the postpartum period were flat/sunken/small nipple (7.7%), pain/tenderness (3.9%), swelling/fullness/engagement (10.8%), redness/temperature change (28.8%), crack/wound/bleeding (26.1%), and mastitis (5.6%).

In addition to modern medicine applications in the treatment of breastfeeding problems, alternative approaches such as tea, lanolin, peppermint, and massage have been extremely beneficial (Arora, Vatsa, & Dadhwal, 2008).

In our study, breast engorgement, breast congestion, mastitis, breast abscess, sunken or flat nipple, nipple pain, and cracks, which are the most problematic breast-related problems in breastfeeding problems, will be explained in detail with their alternative approaches.

Breast Problems During Breastfeeding and Alternate Approaches

Breast Engorgement

Breast engorgement is observed in 2% of lactating mothers (Melton, Stanford, & Dewitt, 2012). On the second and third days after birth, lymphatic ponding in the breast tissue, edema around the milk ducts, and more milk production in the alveoli occur. Engorgement may develop due to insufficient frequency and insufficient amount of breastfeeding, lack of breastfeeding in an appropriate position, excess breast milk, and use of

tight bras (Şen-Oran, Gürdal, & Soybir, 2013; Çaka, Topal, & Altnkaynak, 2017). Engagement is also 3-5. On these days, the breast is hard, full, edematous, and hot, and these symptoms begin to regress within 48 hours. The areola is edematous, the nipple is flat, and it is difficult for the baby to hold the breast (Grossman, 2013; Finer, & Zolna, 2014). In the treatment of breast engorgement; the correction of the breastfeeding method, frequent breastfeeding of the baby without restricting breastfeeding, breast massage and manual milking for non-empty breasts, and the use of analgesics for edema and pain are useful if the cold application is required (Boskabadi, Ramazanzadeh, Zakerihamidi, & Omran, 2014; Kültürsay, Bilgen, & Türkyılmaz, 2014; Aprilina, Krislinggardini, Isnaini, & Suratmi, 2021).

In many literature studies, cabbage leaves applied as cold compresses and hot compresses can be very useful if they are applied correctly, among alternative approaches in the treatment of breast engorgement (Disha, Singh, & Suri, 2015; Masoud, 2018; Kaur, & Saini, 2017; El-Saidy, & Aboushady, 2016; Thomas, Chhugani, & Rahma, 2017). For cold compress, cabbage leaves are kept in the freezer for about 20–30 minutes and then applied to the cleaned breast after breastfeeding. This compress is applied to the breast at room temperature in a bra and is worn once or twice a day for 15–20 minutes. A hot compress is a warm application with a sponge cloth on the breasts after breastfeeding. In practice, the temperature of the water is between 43 °C and 46 °C. It is applied to the breast for 15–20 minutes and the compresses are changed frequently for 1–2 minutes (Disha et al. 2015).

In their study, Disha et al. (2015) investigated the effects of hot compresses and cold cabbage leaves on breast engorgement in 64 mothers with breast engorgement. The Numerical rating pain scale (NRS) and 6-point breast engorgement scale were used in the evaluation. Cold compresses were applied to the breast in the first week, and chilled cabbage leaves were applied twice a day for five days in the second week. Pain intensity was measured with the pain scale. At the end of the intervention, pain intensity and breast density decreased equally in both groups. It has been found that hot compresses and cold cabbage leaf applications are effective in relieving and reducing pain in breast engorgement (Disha et al. 2015). El-Saidy et al. (2016) in a quasi-experimental randomized study conducted with 90 postpartum mothers with breast engorgement; the effects of hot compresses and cold cabbage leaves on breast engorgement were investigated. The six-point breast engorgement assessment scale, the Visual Analogue Scale (VAS), and the LATCH breastfeeding scale were used. The mothers were divided into two equal groups and their scores were evaluated before and after the procedure. A significant difference was found in both groups. It has been determined that application of cold

cabbage leaves is effective in reducing breast engorgement and relieving pain (El-Saidy, & Aboushady, 2016).

Masoud (2018), in his semi-experimental study, examined the effect of cold cabbage leaves on 100 mothers with breast engorgement during lactation; control and experimental groups were formed. A six-point breast engorgement assessment scale, the Visual Analogue Scale (VAS), redness, edema, and the areola circumference assessment scale were used in the study. Breast care and breastfeeding training were given to the control group. The pain score, redness, and edema of both the experimental and control groups were evaluated on the 1st, 3rd, and 5th days. Cabbage leaves were found to be effective in relieving breast engorgement (Masoud, 2018). Kaur et al. (2017) in the semi-experimental study, the effect of cabbage leaves on breast engorgement was investigated in 63 postpartum lactating women (30 control, 33 experimental groups). The control group received standard care, and the experimental group received cold cabbage leaf application. The blind breast engorgement evaluation scale was used in the study. Chilled cabbage leaves were applied to the breast twice daily for three days. It has been observed that the application of cold cabbage leaves is very effective in reducing breast engorgement (Kaur & Saini, 2017).

One of the alternative methods used in breast engorgement is breast massage, and studies in the literature support this practice. Massage can be applied to both breasts for thirty minutes before breastfeeding until the pain subsides (Cho, Ahn, Ahn, Lee, & Hur, 2012; Thomas et al., 2017).

Cho et al. (2012), in a study investigating the effects of Oketani breast massage on breast pain and the sucking speed of babies in postpartum women; 47 postpartum mothers complaining of breast pain were admitted to care in the postpartum care center and were divided into two groups. Breast massage was applied to the experimental group by an Oketani massage therapist, and to the control group, a traditional massage technique was applied by a nurse in the postnatal care center. It was determined that breast pain decreased significantly in both groups. It was determined that the sucking rate of the newborns in the experimental group increased significantly compared to the control group. These findings show that Oketani breast massage is effective in relaxing the breasts (Cho et al., 2012).

Thomas et al (2017) in an experimental study in which 30 mothers with breast engorgement in lactation applied pre-breastfeeding breast massage and correct breastfeeding techniques to 1-3 of the mothers, A significant difference was found between the pre-test and post-test scores on the next day. It was found that after the mothers applied breast massage and proper breastfeeding techniques, breast engorgement improved, their

pain decreased, and they breastfed effectively (Thomas et al., 2017).

Breast Congestion

Breast congestion is seen in 25–85% of breastfeeding mothers. On the third-fourth day after birth, the late and insufficient frequency of breastfeeding is usually due to incorrect breastfeeding positions. Due to insufficient ejaculation, the breast is overly tense, hard, sensitive, and hot (Chaves, Araújo, Santos, Pinotti, & Oliveira, 2012). Mastitis may develop if the breast is not emptied. When emptied, clogging is a temporary problem and decreases over time within 24 hours (Melton et al., 2012).

An alternative approach used in breast congestion is the application of manual breast massage. In the literature, it is seen that massage is a useful practice. Massage should be applied to the breasts before breastfeeding (Witt, Bolman, Kredit, & Vanic, 2016).

Witt et al. (2016) study, 27 mothers with breast congestion during lactation were taken to massage therapy. A breast massage was applied to the mothers for 30 minutes. Breast congestion severity was graded and recorded before and after the massage. Pain and breastfeeding complications of the mothers on the 2nd day, 2nd week, and 12th week were evaluated before and after the procedure. It was observed that the mean score of pain level due to initial breast congestion before receiving breast massage was 6.4. After the massage, it was determined that there was a significant improvement in the mean pain score (6.4 vs. 2.8) due to congestion in both breasts. It has been observed that the massage process helps in reducing acute breast pain due to milk congestion (Witt et al, 2016).

Mastitis

Mastitis is an inflammation of the breast tissue and is seen in 3%–33% of breastfeeding mothers. It mostly occurs within the first 12 weeks after birth, and there is difficulty in breastfeeding and insufficient sucking (Chaves et al., 2012; Rosa, 2010). It occurs due to obstruction of milk ducts, nipple cracks, or bacterial causes. Microorganisms (E. coli, streptococci, staphylococci, etc.) settle in the cracked area of the nipple and cause infection. The breast can also be unilateral or bilateral. Breasts also have redness, tenderness, pain, and fever. Weakness, nausea, and vomiting may also develop. To prevent mastitis from progressing to a breast abscess, the breasts should be emptied with the correct breastfeeding method, breastfeeding should not be interrupted, and fluid intake should be increased (Bilgin & Potur, 2010; Şen-Oran et al., 2013). Hot compresses and analgesics can also be used to reduce pain.

The World Health Organization (WHO) recommends taking antibiotics if there is no change in symptoms even though milk is drained

for 24 hours, if there is a significant nipple crack and if the infection is of bacterial origin (Mastitis: Causes and Management). [http://www.who.int/childadolescentHealth/New_Publications/NUTRITION/WHO_FCH_AH_00_13.PDF]).

Generally, mastitis regresses within the first 48 hours after antibiotic treatment. If the baby does not take milk, the breast should be emptied with a pump. If mastitis recurs, it should be followed up, it should be evacuated surgically with antibiotic treatment, and the mother should be rested. Breastfeeding should be continued, and if it is not possible to breastfeed due to pain, the breast should be emptied every three hours (Şen-Oran et al., 2013; Çaka et al., 2017).

The use of probiotics in the treatment of breast mastitis is an alternative method, and it has been beneficial in the literature study (Arroya et al., 2010). Probiotics are used as an alternative to antibiotics; They are lactobacilli obtained from healthy human milk and strengthen the immune system by showing anti-infectious effects and increasing leukocytes. One is taken orally every day and the treatment lasts an average of 21 days (Arroya et al., 2010).

Arroya et al. (2010) investigated the effect of using lactobacillus as an alternative to antibiotics in 352 mothers who had mastitis during lactation. Mothers were divided into two groups: case and control. In the mothers in the case group, 124 people used Lactobacillus fermentum and 127 people used lactobacillus salaries. In the control group (101 people), an antibiotic treatment used in primary care centers was applied. At the end of the 21-day treatment fever, fewer bacteria were observed in the milk of the probiotic recipients compared to the control group, and lower pain scores and disease recurrence were detected in this group. In the study, it was determined that probiotic lactobacilli could be used as an alternative to antibiotics (Arroya et al., 2010).

Breast Abscess

Although breast abscess is seen in 5–11% of women with mastitis, it develops in the form of a mass when mastitis is not treated well. The disease's symptoms are similar to mastitis. Symptoms include high fever and malaise. The abscess should not be drained manually (Berens, 2015). According to WHO, an abscess should be drained with simple needle aspiration. Abscess fluid should be cultured so that appropriate antibiotic therapy can be started, and antibiotic therapy should be discontinued after three days when the symptoms recede. It should not be breastfed from the affected breast (Mastitis: CausesandManagement.[http://www.who.int/childadolescentHealth/New_Publications/NUTRITION/ WHO_FCH_AH_00_13.PDF]; Sabel, 2009).

Concave/ Flat Nipple

Inverted or flat nipples negatively affect the breastfeeding period. It should be detected and resolved in the prenatal period, and the problem should be resolved the first time after birth. In the early period of breastfeeding, the baby should be allowed to settle on the breast by skin-to-skin contact (Çaka et al., 2017). Regardless of the nipple of the baby, which is well placed on the breast, information should be given that the nipple will become prominent with the negative pressure that occurs while sucking. Anatomical breast molds can be used to remove the sunken nipple (ALUŞ TOKAT, 2009). In this period, until the problem is resolved, breast milk should be expressed in the baby's mouth or the milk should be given with a spoon and the milk should be emptied (Protocol, 2010; Mastitis: CausesandManagement.[http://www.who.int/childadolescentHealth/ New_Publications/NUTRITION/ WHO_FCH_AH_00_13.PDF]).

It is seen in many literature studies that the Hoffman massage technique and silicone breast shields, which are alternative methods used for inverted or flat nipple problems, are beneficial (Manerkar, Mondkar, Goel, 2015; Ponmathi, Mounika, Vijayalakshmi, & VPR, 2017). The Hoffman massage technique is performed three times a day before breastfeeding. Silicone nozzle molds are made of flexible rubber, suitable for anatomical shapes, with a nozzle diameter of 13 mm and a thickness of 0.5 mm. Before breastfeeding, the nipple is thoroughly washed and the breast is moistened a little to adapt to the breast. After each breastfeeding, the silicone breast molds are boiled with soapy water for 10 minutes and then reapplied for 24 hours (Manerkar et al., 2015; Ponmathi et al., 2017). Ponmathi et al. (2017) case report case series study, the effect of the Hoffman technique on a sunken or flat nipple in postpartum women was investigated. Primiparous and multiparous women, aged 25 to 35 years, who had a normal delivery and cesarean section up to the 45th day after delivery were included in the study. A significant difference was found when breastfeeding was evaluated before and after the Hoffman technique test. It was concluded that the Hoffman technique is an effective method for removing the nipple and for breastfeeding quality (Ponmathi et al., 2017).

Manerkar et al. (2015) in their prospective cohort study, the effect of the silicone breast shield was investigated in 30 women with condensed/ flat nipple problems during lactation. The study was conducted with a Likert-type scale. The breast shield application was evaluated on the 7th, 14th, and 28th days. At the end of the study, it was determined that 80% of the mothers breastfed successfully on the postpartum 28th day, their babies gained weight, and they did not feel any pain while using the silicone breast shield (Manerkar et al., 2015).

Nipple Pain and Fissures

Nipple pain and cracking are common in 34–99% of mothers and occur within the first week or two of breastfeeding (Jain, Parmar, Singla, & Azad, 2009). In a study by Almqvist-Tangen et al. (2012), it was reported that mothers who breastfeed less than five times a day (82.9%) experience more nipple-related problems than those who breastfeed 6-10 times (39.2%). Pain caused by nipple cracks reduces breast milk production and secretion, creates stress in the mother, and stops breastfeeding by preventing oxytocin production (Almqvist-Tangen, Bergman, Dahlgren, Roswall, & Alm, 2012; Jackson, & Dennis, 2017).

Causes of nipple pain and cracking; It occurs due to reasons such as delayed breastfeeding after cesarean section, the baby sucking the nipple due to incorrect breastfeeding technique and not separating it from the breast properly, the pressure exerted by the baby's tongue, and the use of excessive breast pumps (Carlander et al., 2010). Protective measures can be taken for pain and cracks in the nipple. These are: the nipple should be washed with plain warm water, soap and other chemicals should not be used, the less painful side should be breastfed while breastfeeding, the baby should be breastfed frequently and for short periods, not only the nipple but also the areola should be in the baby's mouth during breastfeeding, and the use of plastic pads should be avoided. As long as the problem of nipple crack and pain is taken care of, it usually heals at the end of the first week of breastfeeding or up to ten days (Prior et al., 2012).

As complications related to breastfeeding, nipple pain, and trauma are considered among the most important factors affecting the absorption and continuation of breastfeeding in the first weeks of breastfeeding. Since the 17th century, many ointments for the treatment of traumatic nipples have been applied topically to provide comfort to the mother. Today, many studies are carried out on pharmacological and alternative treatments (Niazi et al., 2018).

Some of the alternative methods used after breastfeeding for nipple pain and cracks are lanolin, purslane lotion, peppermint oil, jujube fruit lotion, and aloe vera gel. These alternative methods used have also been found to be useful in literature studies (Jackson & Dennis, 2017; Niazi, Yousefzadeh, Rakhshandeh, & Esmaeily, 2019; Abd-Elsalam, Hamido, & Abd el Hameed, 2011; Niazi et al., 2018; Shanazi et al., 2015; Shahrahmani, Akbari, Mojab, Mirzai, & Shahrahmani, 2018; Tafazoli, Saeedi, Gholami Robatsangi, & Mazloom, 2010).

Lanolin and Purslane

Lanolin creates moist skin and prevents wounds, increases the rate of epithelial tissue, and heals wounds. Lanolin is the active ingredient in

lanolin ester. Esters have anti-inflammatory, anti-bacterial, skin-protective, and wound healing properties, as well as provide a moist environment. When breast tissue is injured, chemicals such as histamine and bradykinin are released at the injury site and cause pain. Lanolin enhances healing by maintaining the moisture of injured tissue. It also relieves pain because it reduces the amount and duration of exposure to these chemicals. Purslane has been introduced as the most widely used herbal medicine by the WHO. It has an anti-inflammatory and sedative effect with flavonoids, tannins, saponins, and terpenoids in its content. Omega 3 in purslane is the most likely agent responsible for the anti-inflammatory effect by reducing inflammatory cytokines. Before using the lanolin and purslane lotion, the nipple and areola are cleaned. It can be applied three times a day or applied to the area in small amounts until the pain subsides. The application period can be between 1-12 weeks (Niazi et al., 2019; Niazi et al., 2018).

In the randomized controlled study by Jackson et al. (2017), the effect of lanolin used in the treatment of nipple cracks and pain in nursing mothers was investigated. The research group was divided into two as lanolin application (93 women) and standard care (93 women). Both groups were taught the correct method of breastfeeding. On the 4th and 7th days of the study, mothers were called by phone and asked about breast pain. Data was collected again at the 4th and 12th weeks and evaluated with the NRS pain rating scale. It has been revealed that lanolin application does not affect nipple pain (Jackson & Dennis, 2017).

Niazi et al. (2017) investigated the effects of lanolin and purslane lotion on nipple pain in 86 breastfeeding women; randomly divided into two equal groups. Both groups were taught the correct method of breastfeeding and its use. The researcher recorded the nipple pain score by measuring it with a numerical pain rating scale on the 3rd and 8th days after treatment. The results showed a significant difference in terms of pain intensity on the 3rd and 8th days in both groups, and pain intensity decreased in both groups. However, it was observed that the pain severity of mothers using purslane lotion was lower than the group using lanolin (Niazi et al., 2019).

Mint oil

Peppermint oil contains carvone, limonene, menthol, and menthone. Menthol has a specific receptor on the cell membrane. This receptor blocks the pain transmission flow and increases the pain threshold. Peppermint oil is effective in reducing the pain in the tissue and in relieving the person. Before using peppermint oil, it is applied to the area in the form of four drops three times a day, two hours apart, after cleaning the nipple and areola. The application period is up to 2 weeks (Abd-Elsalam et al., 2011; Niazi et al., 2018; Shanazi et al., 2015).

Abd-Elsalam et al. (2011) examined pharmacological alternative treatment methods in their study of 200 nursing mothers who were diagnosed with sore nipples by doctors (Abd-Elsalam et al., 2011).

Lanolin application in 100 women, peppermint oil application in 50 women, and tea bags application in 50 women were applied to the nipples of nursing mothers. In the study, the Visual Analogue Scale (VAS) and the nipple crack rating scale were used to evaluate nipple pain. As a result of the study, it was found that peppermint oil may have some beneficial effects in reducing nipple cracking. In addition, moderate or severe pain and areola cracking were not observed in the lanolin or peppermint oil groups. However, moderate pain was seen in those who used tea bags. In the study, it was determined that peppermint oil was more effective in reducing nipple cracking compared to teabag application and lanolin. In addition, depending on the results of the study, alternative therapy was found to be as effective as pharmacological therapy (Abd-Elsalam et al., 2011).

Niazi et al. (2019) investigated the effects of menthol extract (peppermint oil) and breast milk application on nipple crack and pain in the postpartum period. The intervention group (55 women) was asked to apply four drops of menthol extract every two hours, and the control group (55 women) four drops of breast milk. Nipple fissure and pain severity were assessed using the Amir Scale and VAS tool 10 and 14 days before and after treatment, respectively. As a result of the study, it was observed that the application of menthol essence reduced the pain of the nipple and healed the nipple crack better than the application of breast milk (Niazi et al., 2019).

In a double-blind randomized controlled study conducted by Shanazi et al. (2015), the effects of lanolin, peppermint oil, and dexpanthenol reams on nipple cracks were compared in 126 nursing mothers. The mothers were randomly divided into three groups according to the use of lanolin, peppermint oil, and dexpanthenol cream. Nipple pain was evaluated with the Storr scale (NSRS), and nipple fissure was evaluated with the Champion scale (NTS). It was determined that the mean scores of nipple pain and nipple fissure in mothers before the intervention, on the third, seventh, and fourteenth days, did not differ significantly between the three groups. The results of the study revealed that lanolin, peppermint, and dexpanthenol applications have similar therapeutic effects on the traumatic nipple (Shanazi et al., 2015).

Jujube Fruit Lotion

Jujube fruit lotion contains potassium, phosphorus, calcium, zinc, tannins, phenol flavonoids, phenolic acids, protein, and fatty acids. The saponins and polysaccharides in jujube have an important role as an anti-inflammatory. Flavonoids, cyclopeptides, alkaloids, and terpenes in the

content show anti-microbial and anti-inflammatory effects. Jujube fruit lotion is used after cleaning the nipple and areola area after each feeding. It can be applied five times a day for fourteen days (Shahrahmani et al., 2018).

Shahrahmani et al. (2018), the effect of jujube fruit lotion application on nipple cracks in 100 primiparous breastfeeding mothers was investigated. 100 primiparous breastfeeding mothers were divided into experimental and control groups. 0.5 mL of jujube fruit lotion was applied to the mothers in the experimental group. The mothers in the control group were administered 4–5 drops of breast milk five times a day after breastfeeding. In the study, it was evaluated on the 7th and 14th days using the Visual Analogue Scale and the Amir scale. While no significant difference was observed between the two groups on the 7th day, a statistically significant difference was observed between the two groups on the 14th day. As a result of the study, it was observed that the application of jujube fruit lotion healed nipple cracks faster and better than breast milk (Shahrahmani et al., 2018).

Aloe vera Gel

Aloe vera gel contains glucomannan-polysaccharide, carboxypeptidases, glucose, and vitamin combinations. These combinations show antioxidant, antibacterial, antifungal, and anti-inflammatory effects. Flavonoids, anti-inflammatory, vitamins A, C, and salicylic acid are effective in inhibiting the formation of bradykinin and histamine, which play a role in the formation of wounds. Aloe vera gel is applied after cleaning the nipple and areola after each feeding. It is cleaned and reapplied three times a day for a week without drying it (Tafazoli et al., 2010).

Tafazoli et al. (2010), in a study examining the effects of using aloe vera gel and lanolin on 100 mothers with nipple cracks and pain in the postpartum period, the mothers were randomly divided into two equal groups as the experimental group (A. vera gel) and the control (lanolin) group. Correct breastfeeding methods and correct drug use were taught to both groups. Nipple pain and fissure were evaluated with a Storr score on the 3rd and 7th days, and a statistically significant difference was found between them. According to the results, mothers using A. vera gel were found to be more effective on nipple crack and pain than mothers using lanolin lotion (Tafazoli et al., 2010). Silver cap application is one of the alternative methods used for nipple pain and cracks and has been useful in the literature study (Marrazzu et al., 2015).

Silver Cover

Silver is a natural agent with anti-bacterial and anti-inflammatory properties. After the silver particles adhere to the cell membrane

surface of the bacteria, they destroy the respiratory system and produce hydrogen peroxide, which kills the bacteria. It also prevents the entry of microorganisms into the wound area. It creates a moist environment on the wound surface, ensures the proliferation of epithelial cells in the affected area, and creates an indirect healing effect. The silver cap does not contain any substances, unlike lotions, and does not change the taste of breast milk. After breastfeeding, the nipples are gently washed or wiped, and the cups are placed directly on the nipple and fixed with a bra. It can be applied to the area for 24 hours after cleaning with water (Marrazzu et al., 2015).

In the study by Marrazzu et al. (2015), the effect of the silver cap on nipple fissure and pain in nursing mothers was investigated. The mothers were randomly divided into two groups: the intervention group (20 women) and the control group (20 women). The control group was recommended to receive standard care (personal hygiene protection and nipple care) with breast milk application to the nipple crack and areola after each feeding. The silver cap was applied to the nipple crack and areola in the intervention group. Correct breastfeeding methods were taught to both groups. The study was completed at 15 days and evaluated with the NRS pain scale on days 0, 2, 7, and 15. The silver cap was found to be more effective than standard care for reducing and healing nipple fissures (Marrazzu et al., 2015).

One of the alternative methods used for nipple cracks and pain is phototherapy application. The usefulness of the application was determined by the literature study (Chaves, Araújo, Santos, Pinotti, & Oliveira, 2012).

Phototherapy

Phototherapy is a tool that uses low-intensity near-infrared red light with a wavelength in the range of 630 to 1000 nm. Phototherapy increases fibroblasts and collagen synthesis, which provides tissue regeneration and accelerates wound healing. While providing wound healing, it also has an analgesic effect. Phototherapy uses a prototype apparatus compatible with the nipple and areola and an applicator to diffuse the light. Before the application, glasses are put on the person, and the nipple and areola area are cleaned. After the apparatus is placed on the nipple and areola and fixed with a bra, light is given to the area where the apparatus is located with the applicator. It is applied to the area twice a week for four weeks and then in eight sessions after breastfeeding (Chaves et al., 2012).

In a pilot study conducted by Chaves et al. (2012), the effect of phototherapy was investigated in 19 lactating women with nipple cracks and pain. Mothers were divided into control (10 people) and experimental groups (9 people). Placebo phototherapy was applied to the control group and phototherapy to the experimental group. Both groups received

standard care. Pain intensity was measured with the 11-point Pain Intensity Numerical Rating Scale at all treatment sessions before and after phototherapy. It was observed that the nipple crack completely healed after four sessions of phototherapy treatment in the mothers in the experimental group, and the same improvement was achieved in the control group in the eighth session. Although the severity of nipple pain decreased in both groups, this decrease was found to be significant only in the experimental group (Chaves et al., 2012). Low-level laser therapy is an alternative method used for nipple pain and fissures, and it was found to be beneficial in the literature study (Coca et al., 2016).

Low-Level Laser Therapy

The low-level laser is called a biostimulant. The biological effect of laser therapy is that it increases the blood flow rate through vascular dilation, changes the hydrostatic pressure in the capillaries, and plays an important role in strengthening the immune system. In addition, it stimulates the growth of fibroblasts and increases collagen synthesis, providing wound healing and reducing pain and inflammation. The low-level laser is applied such that the 40-milliwatt red laser beam is emitted into three consecutive spots (middle, left, and right) at the nozzle tip. It is performed after breastfeeding in three sessions (0, 24, and 48 hours) after wearing glasses and cleaning the nipple and surrounding area before the application (Coca et al., 2016).

Coca et al. (2016) conducted a study in Sao Paulo59 showing the effects of low-level laser on the severity of breast pain in nursing mothers. Low-level laser treatment was applied to the experimental group (30 people), and the low-power red light was applied to the control group (29 people). The VAS scale was used to measure the nipple pain level of mothers during breastfeeding. At the end of the three sessions, there was a statistically significant difference in the severity of nipple pain in the mothers in the experimental group, but there was no significant difference in the control group. The results of the study showed that the pain during breastfeeding was greatly reduced in groups using low-intensity laser therapy, and it could be a good option for the healing of nipple cracks (Coca et al., 2016).

Conclusions

The majority of breastfeeding women experience breast problems at the beginning of breastfeeding. The most common breast problems related to breastfeeding are breast fullness (engagement), breast engorgement, mastitis, breast abscess, recessed or flat nipple, nipple pain, and cracks. Because of these problems, mothers can stop breastfeeding. It is seen that alternative treatments for breast problems during breastfeeding are applied effectively and provide benefits. Cold cabbage leaf application, which is

mostly used for breast fullness, is effective in improving breast engorgement and reducing pain. Manual breast massage in breast occlusion reduces the pain associated with milk occlusion. The probiotic lactobacillus used for mastitis problems prevents recurrence of mastitis and reduces pain in the breast. The silicone breast shield, which is generally used on the inverted/flat nipple, removes the nipple and increases the quality of breastfeeding. Nipple pain and cracks, mostly lanolin and peppermint oil, reduce nipple pain and heal the nipple.

However, studies on alternative treatments used for breast problems are limited and more evidence-based studies are needed. Since women have difficulties coping with breast problems during this period, they need counseling on breastfeeding and breast care. Therefore, midwives have a great responsibility. Midwives should inform women about correct breastfeeding methods and breast care in the antenatal period. In addition, they should also include training on alternative approaches to breast problems in the postpartum period.

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CHAPTER 16

THE ROLE OF CYTOKINES IN CANCER

Ferah CÖMERT ÖNDER[1]

1 Assistant Professor Dr. Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Medical Biology. ORCID ID: 0000-0002-4037-1979

1. INTRODUCTION

Cancer is a global problem and is the second leading cause of death worldwide (Siegel et al. 2021). Among various cancers such as breast, pancreas, prostate, liver, lung, colon, and stomach cancers are identified as major causes of deaths (Chakraborty et al. 2020). It has been reported that inflammation-related infections have affected the cancer types and can cause as fundamental reason for 15-20% of deaths from cancers (Coussens and Werb 2002). Concerning the hypothesis of Rudolf Virchow, cancer was associated with inflammation for the first time in 1863 (Balkwill and Mantovani 2001). It was indicated that all cancer cases (approximately 25%) worldwide were affected by chronic infection with inflammation (Diakos et al. 2014). It is reported that cancer-related inflammation (CRI) is triggered by many factors such as chemokines and cytokines. However, inflammatory cytokines play a role as a biomarker to detect cancer (Chakraborty et al. 2020). The main tumor microenvironment (TME) constituents that participate in CRI are inflammatory cell types. However, TME includes different cell types such as stromal cells, cancer-associated fibroblasts, and tumor-associated macrophages (Masjedi et al. 2021).

To induce tumor growth and develop resistance against chemotherapy, secreted cytokines and growth factors contribute to contract of tumor cells with other cells (Comen et al. 2018). The cytokines are a group of soluble glycoproteins and peptide molecules with low molecular weight that mediate cell-to-cell communication (Dunlop and Campbell 2000; Landskron et al. 2014). They are synthesized by endothelial and fibroblast cells to regulate cell survival, proliferation, differentiation, cell migration and cell death (Landskron et al. 2014). The interactions between the cells are mediated by the cytokines thus cell and tissue functions are regulated (Dunlop and Campbell 2000). The cytokines possess a role in several processes such as cell growth, immune response, and wound healing. Some cytokines are produced by the secretory pathways in all human cells. Some cytokines bind to cell membrane and extracellular membrane. The main cytokines are known interleukins (ILs) including IL-1, IL-6, IL-17, and IL-23, and transforming growth factor (TGF-β, growth factors, and colony-stimulating factors, and tumor necrosis factor (TNF-α) (Chakraborty et al. 2020).

This chapter focused on the role of cancer-related cytokines in various human cancers with cancer progression, development, regulation, metastasis, proliferation, and growth.

2. THE ROLE OF CYTOKINES IN CANCER

Cytokines are relevant to regulation of cancer spread, and growth. Cancer cells can produce the cytokines. The cytokines can display a

behavior on the cancer cell in an autocrine way to generate an environment for growth of cancer. In addition, normal cells including endothelial cells and tumor-associated macrophages are triggered by the cytokines to produce additional cytokines. Some of the cytokines are related to the numerous cancer types (Dunlop and Campbell 2000).

2.1. Uncontrolled Growth and Metastatic Spread

It has been reported that pro-inflammatory cytokines possess cytotoxic and cytostatic effects, however, some of the examples of solid tumors that occasionally proliferate in an autocrine fashion in response to IL-1, IL-2, and IL-6. Furthermore, the TNF gene is expressed in approximately 70% of ovarian cancer biopsies (Naylor et al. 1993). TNF receptors are correlated with tumor cells (Dunlop and Campbell 2000). Cytokines are used by some cancers to stimulate other cells to produce growth factors. As an example, monocyte chemoattractant protein-1 that the reason for the accumulation of TAM, is produced by epithelial ovarian tumor cells. Stimulating of cancer growth via TAM has been described producing of IL-1, IL-6, TNF, and TNG-β etc.. Cytokines play a significant role to activate normal cells producing tumor growth factor following the encouragement of adhesion for tumor cells in the metastatic site. Tumor cells produce IL-1 that increment releasing of soluble intercellular adhesions. Moreover, colon cancer cells produce carcinoembryonic antigen (CEA) and then it binds to receptors to alert the generation of TNF-α, IL-1, and IL-6 that facilitate the colon cancer cells adhesion. The motility of breast cancer can be supported by IL-6. TNF-α and interferon-γ (IFN-γ) can rise pulmonary metastasis in animal models via down regulation of suppressor genes (Dunlop and Campbell 2000; Negus et al. 1995).

2.2. Cancer and Cytokines

Cytokines in increased numbers are associated with malignancies and in increased levels including IL-1, IL-6, TNF, FGF, TGF, G-CSF (granulocyte-macrophage colony stimulating factor) have been identified in cancer patients. Multiple cytokines were detected in the studies. TNF, FGF, and TGF were enhanced at early-stage with cancer patients, increased levels of G-CSF, angiogenin, and TNF-α were detected in patients. According to a comparison study of endometrial cancer patients with control group, IL-2, IL-7, IL-8, IL-10, FGF, TNF, GM-CSF, angiogenin, and TGF-β were importantly increased in patients in the early stage (Dunlop and Campbell 2000).

2.2.1. Interleukin 1 (IL-1)

Interleukin 1 (IL-1) has been defined as an important pro-inflammatory cytokine in medicine. IL-1 consists of two isoforms including IL-1α and

IL-1β which mechanism of inflammatory signaling pathway are more complicated compared to TNF-α (England et al. 2014). IL-1β levels increase in different tumors such as breast, colon, and melanoma. It is associated with poor prognosis in patient-derived studies (Van Gorp and Lamkanfi 2019). IL-1β is directly produced by cancer cells. Tumor promoting effects are proven during cancer metastasis and tumor angiogenesis and this is the evidence that it has cancer suppressive effect (Haabeth et al. 2012). The gene expression that mediates cancer and inflammation is modulated by IL-1 (Kasza, 2013). There is a correlation between tumorigenesis and inflammation that is used for the current therapeutic approaches (Chakraborty et al. 2020). An increased expression level of IL-, NF-κB, and miR181a in colon cancer was reported by Hai Ping et al (Hai et al. 2016). miR181a expression is induced by IL-1β via the signaling pathway of NF-kB and miR181a promoted the cell proliferation with repression of PTEN that is a significant tumor suppressor and constantly mutated in diverse cancers (Chakraborty et al. 2020). It was reported that miR425 expression was upregulated in gastric cancer cells by IL-1β (Ma et al. 2014). Moreover, miR-101 was downregulated by IL-1β that was induced by silica particle and then, induced-IL-1beta increased enhancers of zeste homolog 2 (EZH2) expression, promoting cell proliferation in Xuanwei lung adenocarcinoma cells (Lei et al. 2015). Furthermore, elevated levels of IL-1β have been detected in NSCLC (non-small cell lung cancer) patients. miR101 expression is repressed by IL-1β and related IL-1β/miR-101/Lin28B pathway promotes migration and cell proliferation of NSCLC. Consequently, this pathway can lead to understand of inflammation-promoted tumorigenesis. Additionally, although IL-18 is a member of the pro-inflammatory IL-1β family, it shows some differences in biological functions (Van Gorp and Lamkanfi 2019). Elevated levels of IL-18 have been determined in cancers including breast, gastrointestinal tract cancers, and associated with poor prognosis so it shows a pro-tumorigenic role. It has been reported that there is a negative prognosis between the levels of IL-18 and TNBC patients (Park et al. 2017).

2.2.2. Interleukin 6 (IL-6)

Interleukin 6 (IL-6) is one of the proinflammatory cytokines and has a typical pro-tumorigenic effect. IL-6 plays a role in cancer progression (Taniguchi and Karin 2014). Breast cancer cells produce IL-6 that stimulates proliferation and more aggressive phenotype in ER positive cells (Sasser et al. 2007). IL-6 that induces MCF-7 cell growth, is secreted from fibroblasts of breast tissue (Studebaker et al. 2008). The overexpression of this cytokine in ER+ breast cancer cells (MCF-7) induces epithelial-mesenchymal transition (Sullivan et al. 2009). High IL-6 levels of serum were defined in patients with cancers on the contrary of healthy people and

patients (Landskron et al. 2014; Mitsunaga et al. 2013). IL-6 possesses a role to promote proliferation and inhibit apoptosis and thus, activates JAK/STAT signaling pathway of JAK (Janus kinases) and STATs including STAT1 and STAT3 (Hodge et al. 2005). The studies showed that the impact of IL-6/JAK/STAT pathway depended on the progression and initiation of cancer (Landskron et al. 2014). Inducing of tumorigenesis by IL-6 has been reported for cancers. Moreover, IL-6 is produced initially in a gastric cancer mouse model (Kinoshita et al. 2013). IL-6 can block IL-6R/STAT3 pathway and play a role in the development of multiple myeloma (Chatterjee et al 2004). Due to these findings, there has been an increasing interest to understand IL-6 as a therapeutic target in cancer. Moreover, in prostate cancer cell lines, the effect of miR-21 and IL-6 on the expression of programmed cell death 4 (PDCD4) gene has been investigated. PDCD4 expression can be reduced by miR-21 expressing IL-6 in prostate cancer cells (Dong et al. 2015). It has been reported that downregulation of IL-6 secretion and signaling of NF-κB can help to control tumorigenicity and inflammation by miR-26. IL-6 30 UTR is targeted by miR-26 and the expression of IL-6 is silenced in A549 cells. Thus, miRNAs may act as a cytokine silencer (Chakraborty et al. 2020). It has been indicated that there is an opposite correlation between miR-26a expression and IL-6 in hepatocellular carcinoma (Zhang et al. 2013). It is shown that IL-6/STAT3 signaling is inhibited by miR-26a. Thus, G1/S can be blocked and apoptosis in HCC is promoted (Yang et al. 2013). Inflammatory cytokines are liable for the induction of tumors and the risk in cancer may be restricted with the increase of anti-inflammatory cytokines and decrease signaling pathways activation. The overexpression of IL-6 and IL-8 have been identified with poor prognosis in TNBC patients (Hartmann et al. 2013). Targeting of IL-6 and TNF-α can reduce metastatic cancer. Tumor cells produce TNF-α, ILs-(6 and 8), and IL-1beta that possess pro-tumorigenic properties and immune cells activate them in TME (Powell et al. 2021).

2.2.3. Tumor Necrosis Factor (TNF-α)

Tumor necrosis factor (TNF-α) as a potent cytokine that acts as an inflammatory mediator has been involved in carcinogenesis (Chakraborty et al. 2020; Popa et al. 2007). TNF-α becomes highly considerable at the early-stage carcinogenesis compared to carcinogenesis progression (Moore et al. 2006). TNF-α is extremely expressed in breast cancer (BC) cells. The axis of TNF-α/NF-kB stimulates the malignant attitude in BC cells (Esquivel-Velázquez et al. 2014). Breast cancer tumor growth is promoted by permanent expression of TNF-α (Kamel et al. 2012). The production of low constant TNF-α levels causes a tumor phenotype. Tumor promotion mechanism of TNF-α is relevant to reactive oxygen (ROS) and reactive nitrogen (RNS) species production that makes easy tumorigenesis (Woo et

al. 2000). TNF-α mediated inflammation is related to cancer. When TNF-α associated tumorigenesis has been investigated, the results have shown precancerous like functional and structural changes. TNF-α-elevated levels-based patient derived studies have been reported (Balkwill 2006; Ohri et al. 2010). Cytokines regulate immune cells in TME, and immune cells control progression of cancer. It was demonstrated that miRNAs can regulate the genes that are related with different cytokines secretion (Chakraborty et al. 2020). miR-145 as a tumor suppressor, is responsible for the pathogenesis of CRI, is downregulated in multiple cancers such as triple negative breast cancer (TNBC). Zheng et al has reported that miR-145 is overexpressed in TNF-α treated TNBC cell lines, therefore, it is resulted from apoptosis and induced cell death (Zheng et al. 2016). High levels of TNF-α were detected in patients with B cell chronic lymphocytic leukemia (CLL) (Bojarska-Junak et al. 2002), TNF/TNFR gene in CLL is regulated by some miRNAs and this may be a possible target for leukemia. The progression of colorectal cancer (CRC) is correlated with TNF-α elevating levels in CRC patients (Chakraborty et al. 2020). In addition, it was reported that upregulation of TNF-α with miR-21-mediated possesses a favorable impact on cell proliferation of HeLa cervical cancer, whereas there was no effect on cell apoptosis (Xu et al. 2015).

2.2.4. Transforming Growth Factor β (TGF-β)

TGF-β is a vigorous cytokine with its anti-inflammatory and immune suppressing properties, possesses a role in differentiation, cell proliferation, adhesion, apoptosis (Chakraborty et al. 2020; Esquivel-Velázquez et al. 2014; Santibañez et al. 2011). The acting of TGF-β in cancer is complicated, changing by stage of tumorigenesis and cell type. In initial stages, TGF-β inhibits cell cycle progression and encourage of apoptosis, behaves as a tumor suppressor. TGF-β induces EMT and thus invasion and metastasis are increased (Esquivel-Velázquez et al. 2014; Morrison et al. 2013). In the induction of cancer, TGF-β displays a tumor suppressor effect via the p21 upregulation of cyclin-dependent kinase inhibitor and downregulation of c-Myc (Malliri et al. 1996). The studies have been reported showing that deficiencies in the TGF-β pathway contribute to tumorigenesis (Esquivel-Velázquez et al. 2014; Guasch et al. 2007). It is indicated that the changings in TGF-β signaling take a part in cancer. Elevated levels of TGF-β1 mRNA and protein were reported in various cancers such as colorectal, prostate, and gastric carcinoma. TGF-β receptor mutations are related to breast, bladder, prostate, colorectal cancers (Bierie et al. 2006; Levy and Hill 2006). Cancer is one of the main TGF-β sources in the TME. Bone matrix is a rich TGF-β source in several cancer types. Therefore, this is correlated to promote of tumor and to invasive effects of this cytokine. The results have showed that targeting of this cytokine indicates promising findings

in clinical and preclinical studies in advanced cancer patients (Connolly et al. 2012). According to miR-based studies, TGF-β-1-induced EMT is inhibited by miR-16 in NSCLC cells. TGF-β shows an impact on cancer cell propagation in BC cells (Esquivel-Velázquez et al. 2014). TGF-β1 can be upregulated by miR-106b in invasive BC cells (Gong et al. 2015). TGF-β is related to tumor metastasis via miRNA expression. For instance, miR-182 can be given as a key molecule to regulate cancer development (Qiu et al. 2014).

2.2.5. Interleukin 10 (IL-10)

Various immune cells produce IL-10, which is a strong anti-inflammatory cytokine. It is secreted by tumor cells. Pro- and antitumoral effects of IL-10 have been reported in several studies. NF-κB signaling is inhibited by IL-10 that acts as an antitumoral cytokine by downregulating pro-inflammatory cytokine expression (Landskron et al. 2014). The studies have shown that B cell lymphoma with poor prognosis and expression with tumor cells have been determined with increased levels of IL-10. IL-10 plays a role in breast carcinogenesis. It supports tumor cell proliferation and metastasis (Sheikhpour et al. 2018).

2.2.6. Interleukins (IL-17, IL-19, IL-20, IL-23)

Th17 cells produce IL-17 (also called as IL-17A) that is related to proliferation, metastasis, and invasion of BC cells, and is an important pro-inflammatory cytokine (Esquivel-Velázquez et al. 2014; Song et al. 2021). Thus, it is known for its poor prognosis with BC patients (Song et al. 2021). Recent study has shown that IL-17 has been relevant to programmed death ligand 1 (PD-L1) in BC (Shuai et al. 2020). ILs-(17 and 6) work coordinately to activate STAT3 and then the proliferation of BC cells occurs (Kaur et al. 2018). IL-19, IL-20, and IL-23 play a role in breast tumorigenesis and tumor progression and IL-19 supplies a microenvironment via autocrine effect (Esquivel-Velázquez et al. 2014). The cancer cell proliferation and migration increase with IL-20 and thus a microenvironment has occurred (Hsu et al 2012). IL-23 has an influence in inflammation and angiogenesis in TME (Chakraborty et al. 2020; Langowski et al. 2006).

2.2.7. Granulocyte macrophage colony-stimulating factor (GM-CSF)

GM-CSF is a pro-inflammatory and monomeric cytokine, and it shows a significant role in the development of cancer. Tumors secrete GM-CSF to regulate inflammation in TME. It was reported that changes in GM-CSF related signaling pathways consequence with acute myeloid leukemia (Testa et al. 2002). The role of GM-CSF has been reported in various studies including miRNAs, targets, and signaling pathways (Kornbla et al.

2010; Santamaria et al. 2009).

2.2.8. Interferon-γ (IFN-γ)

IFN-γ is a single member of type II interferon family. It orchestrates pro-tumorigenic and antitumor immunity in TME. IFN-γ is known as a cytotoxic cytokine together with related protease and protein initiating apoptosis in tumor cells. It is indicated that the relationship between IFN-γ and its receptor activates JAKs. The studies showed that IFN-γ affects several cancers with its antitumor potency. IFN-γ is known as a prototypical antitumor cytokine in cancer biology (Mojic et al. 2018). IFN-γ with low dose at tumor site contribute to improve tumor metastasis during immunotherapy (Jorgovanovic et al. 2020).

3. CONCLUSION

Herein, this chapter suggests that the initiation, promotion, angiogenesis, and metastasis in tumors are substantially relevant to inflammation. Cytokines have a crucial role in the development and regulation in various cancers. Thus, this study may lead to new avenues for the suggestion of novel therapeutic approaches to cancer-related mechanisms in signaling pathways.

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CHAPTER 17

NEUROPHYSIOLOGICAL PERSPECTIVE ON APPETITE REGULATION

Gonul Gurol CIFTCI[1] Ebrar Zisan Erdem[2]
Nawar Imad Ahmed[3] Ayse Betul Cingoz[4]

1 ORCID: 0000-0001-5343-9189 Associate Professor, Sakarya University, Department of Medical Physiology, Faculty of Medicine, Adapazari/Sakarya/Turkey gonulgurol@sakarya.edu.tr
2 ORCID: 0000-0003-3550-2732 Sakarya University, Department of Medical Physiology, Faculty of Medicine, Adapazari/Sakarya/Turkey zisan.erdem@ogr.sakarya.edu.tr
3 ORCID: 0000-0002-0635-1851 Sakarya University, Department of Medical Physiology, Faculty of Medicine, Adapazari/Sakarya/Turkey imad.ahmed@ogr.sakarya.edu.tr
4 ORCID: 0000-0002-3207-2039 Sakarya University, Department of Medical Physiology, Faculty of Medicine, Adapazari/Sakarya/Turkey ayse.cingoz@ogr.sakarya.edu.tr

According to 2016 data released by the World Health Organization, more than 1.9 billion adults, 18 years and older, were overweight. Of these, over 650 million were obese; unfortunately, this number is increasing daily (Kristensen et al., 2022). Today, it affects almost all mechanisms of the human body and causes significant metabolic, psychological, and behavioral disorders such as diabetes, cardiovascular diseases, metabolic syndrome, eating disorders (Rhee E. J., 2022). Of course, these situations are shaped under the influence of characteristics such as sociocultural, socioeconomic, genetic, epigenetic, gender, age among individuals. However, changes in the energy balance may also be due to differences in hormonal status, depending on the gender, the diet applied between people.

Central and peripheral changes in the serotonin (5-hydroxytryptamine, 5-HT) system with diet are due to the diversity of serotonin receptors synthesized in the hypothalamus. At least 14 types of 5-HT receptors are known, among which the expression of 5-HT2CRs has been found to be inversely proportional to the level of Leptin, a 16 kDa polypeptide encoded by Ob genes in plasma (Zhou and Cunningham, et al. 2019, Vohra et al., 2021). Seratonin agonists reduce food intake. It has been shown that 5-HT1A, 5-HT2C, and 5-HT1B serotonin receptors in orexinergic neurons are closely related to obesity. The interaction of 5-HT1BR with serotonin agonists reduces feeding via gamma-aminobutyric acid (GABA) ergic interneurons. The same effect was confirmed by increased satiety of mice after administration of the 5-HT agonist d-fenfluramine (Romanova et al., 2018). Fluoxetine (FLX), a selective 5-HT reuptake inhibitor (SSRI), reduces weight gain by affecting the expression of satiety-related neuropeptides in the hypothalamus (Mavanji at al., 2022).

It is known that the effects of 5-HT and dopamine (DA) on feeding behavior are closely related to the individual's mood (Romano et al., 2018). Studies have shown that DA and 5-HT signaling pathways can affect the activity of proopiomelanocortin (POMC) neurons (Romano et al., 2018). The release of DA from neurons in the ventral tegmental area causes it to bind to DA receptors such as D1 or D2 in the nucleus accumbens and prefrontal cortex in reward-related food intake (Fig IB). D1R interaction inhibits dopaminergic and GABAergic neurons in the ventral tegmental area (VTA) via GABA receptors. DA neurons in the substantia nigra, which are also reflected in the dorsal striatum, play an active role in increasing food-related reward behavior (Li et al., 2021). When the connections of the mesocorticolimbic and mesostriatal DA systems with α-melanocyte-stimulating hormone (α-MSH) and Agouti-related peptide (AgRP) were investigated, it was found that α-MSH increases DA transmission and is effective in feeding behavior, and it is even suggested that dopaminergic systems may be effective in the treatment of obesity (Roseberry et al., 2015). Today, unfortunately,

it is still complicated to define the neurophysiological mechanism of homoeostatic or nonhomoestatic systems of impulses that do not last long, such as appetite, in the central nervous system (Imoto et al., 2021).

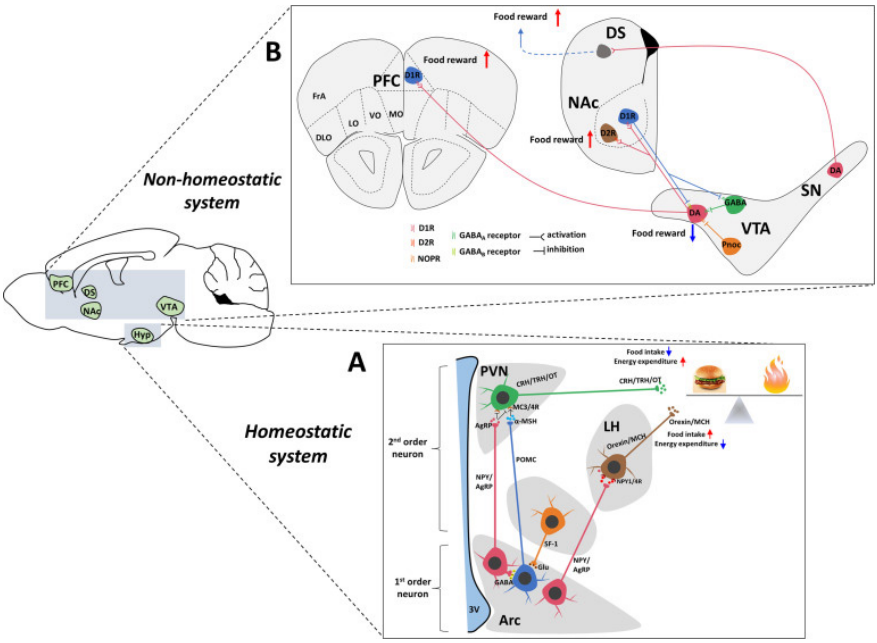

Figure I. Homeostatic and non-homeostatic regulation of appetite in the central nervous system (Li et all., 2021).

Hyp, hypothalamus; Arc, arcuate nucleus; LHA, lateral hypothalamus area; PVN, paraventricular nucleus of the hypothalamus; VMH, ventromedial hypothalamus; 3V, 3rd ventricle; VTA, ventral tegmental area; NAc, nucleus accumbens; PFC, prefrontal cortex; DS, dorsal striatum; SN, substantia nigra; AgRP, agouti-related peptide; NPY, neuropeptide Y; POMC, proopiomelanocortin; Glu, glutamate; GABA, gamma-aminobutyric acid; MCH, melanin-concentrating hormone; α-MSH, α-melanocyte-stimulating hormone; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; OT, oxytocin; DA, dopamine; D1R, dopamine 1 receptor; NOPR, nociceptin opioid peptide receptor

We can say that the concept of appetite, which has been studied since the 18th century, expresses the urge for the food we want to consume (Williams, E.A., 2020). The hunger or satiety drive is coordinated with the regulation and integration of the response to signals produced from the periphery, which may be short and long-lasting. This situation is regulated in the central nervous system through a homoeostatic or nonhomoestatic control shaped by the presence of fatty/sugar tasty foods and the regulation of energy metabolism (Li et al., 2021). Many emotional and behavioral data

such as the appearance, taste, and aroma of food are also included in this arrangement. The importance of the central nervous system in regulating these given sensory signals emerges. Although the hypothalamic areas for satiety (ventromedial nucleus) and hunger (lateral hypothalamus) were defined by Hetherington and Ranson in the 1940s, the neural mechanisms and related processes of homeostasis today are among the leading research topics (Uwaifo G.I., 2021).

It covers all processes, such as the modulation of neural circuits in the hypothalamus, a regulatory center in the concept of appetite, and in healthy behavior or energy balance, which can cause differences between individuals. These processes are also related to the interactions of the hypothalamus on the endocrine system, its connections with the gastrointestinal system and adipocytes. Orexigenics such as ghrelin secreted from the gastrointestinal tract, neuropeptide Y (NPY), AgRP, orexin, galanin (Gal), corticotropin-releasing hormone (CRH), as well as Leptin, Nesfatin-1, peptide YY (PYY), cholecystokinin (CCK), oxyntomodulin (OXM), glucagon-like peptide-1 (GLP-1), GABA, amylin, melanin-concentrating hormone (MCH), cocaine and amphetamibe-related transcript (CART), POMC, and Pancreatic polypeptide Anorexigenics (Table I) such as (PP) regulate appetite (Adan et al., 2006; Assan et al., 2021; Austin and Marks, 2008; Mhaibes et al., 2021; Pliquett et al., 2006; Sakurai, 2007) . Leptin, nesfatin, adiponectin, resistin, and amylin, associated with adipose tissue, are anorexinergic (Delgado Teresa, 2013). Production sites of orexogenic and anorexigenic substances, receptor distributions, and appetite effects differ. The secretion of orexigenic Ghrelin from the stomach increases NPY/AgRP neurons, which stimulates feeding, while AgRP neurons in the hypothalamus contribute to the inhibition of NPY-mediated POMC neurons and support food intake. In addition, Orexin A from the orexigenic receptor and MCH receptors such as MC1, MC2, MC3, MC4, and MC 5 are associated with increased food intake (Baldini ve Phelan, 2019, Vohra et al., 2021). Leptin hormone is secreted from adipocytes, OXM, CKK, and GLP-1 from the intestine, PP and Amylin are substances that inhibit food intake by reducing appetite with an anorexigenic effect. Neurons in the hypothalamus such as Nefsatin-1, CRH, CART, and POMC/α MSH also show a suppressive effect on food intake (Vohra et al., 2021).

Table 1. Effects and properties of orexigenic and anorexigenic substances on appetite (Adan et al., 2006, Pliquett et al., 2006, Sakurai, T., 2007, Austin ve Marks, 2008, Gioldasi et al., 2019, Assan et al., 2021, Mhaibes et al., 2021, Sonne et al., 2021).

Effect on food intake or action	Substance	Production, Location	Receptor	Effect on food intake or action
Orexigenic	Ghrelin	Stomach Gastric K-cell, gut	Ghrelin receptor, CHR-1a	Stimulating feeding by increasing NPY/AgRP and antagonizing leptin effects
	Neuropeptide Y	Medial arcuate nucleus and CNS	Y1, Y5	Stimulating feeding and antagonizing POMC action
	AgRP	Brain, Medial arcuate nucleus	MC3R, MC4R antagonist	Stimulating feeding, inhibit POMC neurons by antagonistic actions of GABA and NPY
	Orexin	Hypothalamus	Orexin A	Promote feeding
	Galanin (Gal)	Gastrointestinal tract and hypothalamus		Stimulate food intake
	MCH	Brainstem, hypothalamus	MC1, MC2, MC3 MC4 and MC 5	Stimulate food intake
	Leptin	Adipose tissue	Leptin receptor-Rb	İnhibiting NPY and AgRP and stimulating POMC and CART inhibiting feeding
	Nesfatin-1	Hypothalamus, Vagal nerve, Brain stem	Melanocortin receptor	Decrease appetite
	Peptide YY	İleum, colon, rectum	Y2	Decrease gastric emptying ve intestinal motility
	CCK	Duodenum, jejunum	CCK-A, CCK-B	Decrease appetite, increase gallbladder emptying, decrease gastric emptying
	OXM	Distal ileum and colon	GLP-1, glucagon	Suppression of ghrelin
Anorexigenic	GLP-1	Duodenal L cells, Distal ileum and colon	GLP-1	Increase insulin release, decrease gastric acid secretion, decrease appetite
	GABA	Hypothalamus	$GABA_A$, GABAB	Decrease food intake
	Amylin	Pancreatic β cell	AMY_{1-R}, AMY_{2-R}, AMY_{3-R}	Decrease appetite
	CRH	Hypothalamus	CRH1, CRH2	İnhibit food intake
	CART	Arcuate nucleus	Has not been discovered yet.	İnhibit food intake
	POMC/α MSH	Arcuate nucleus	MC3R, MC4R	Decrease appetite
	PP	Pancreas	Y4	Decrease appetite

In the studies carried out to date, the structures in the arcuate nucleus defined as two parts as ventromedial (orexigenic path) and dorsolateral (anorexigenic way) are related to NPY and AgRP in the ventromedial part (Fig IA.). In contrast, the role in the dorsolateral part is POMC/CART has been shown to be associated with the leptin-melanocortin pathway (Li et al., 2021). Moreover, it is stated that α-MSH, which is a product of the POMC gene that acts with melanocortin-4 receptors (Mc4R) in the anorexigenic pathway, is formed by the degradation of POMC by prohormone convertase (PC1) (Suzanne M. Appleyard, 2003). As a result, it is stated that neuropeptides in AgRP in stimulating food intake in the arcuate nucleus and NPY have an antagonistic effect on preventing the binding of members of the melanocortin system, leading to hunger (Vohra et al., 2022).

Serotonergic compounds cause the release of MSH over POMC neurons (Mavanji et al., 2022). α-MSH, γMSH, and β-endorphin, an endogenous opioid, are the main products of the POMC gene. In addition, these intermediates are found in the arcuate nucleus (ARC), which is located in the third ventral layer of the tuberal hypothalamus and acts as a modulator. The ARC is located close to the median eminence (ME) circumventricular region, and therefore its proximity to the blood-brain barrier (BBB) causes it to receive environmental stimuli via CSF, thus regulating the creation of integrative responses in the brain. Recent studies have shown that disorders in BBB development, which may affect ME, may lead to obesity (Fig 2). It has been shown that organizational changes in tight junction proteins that make up the BBB are at the expression level in structural changes of brain tissue such as hunger, metabolic changes, and trauma. In addition to observing this situation in long-term fasting periods, it has been found that the access of molecules such as Leptin to this region in the hypothalamus increases (Suzanne M. Appleyard, 2003, Rijnsburger et al., 2019, Vohra et al., 2022). It is interpreted that 85% of the total leptin amounts in obese people are found in free form in the circulation, which may be related to the higher absolute Leptin amount in the Cerebro Spinal Fluid (CSF) of obese people compared to lean people. Likewise, it has been proven by the in situ brain perfusion method that leptin transmission from the BBB of obese mice is reduced (Cui et al., 2017).

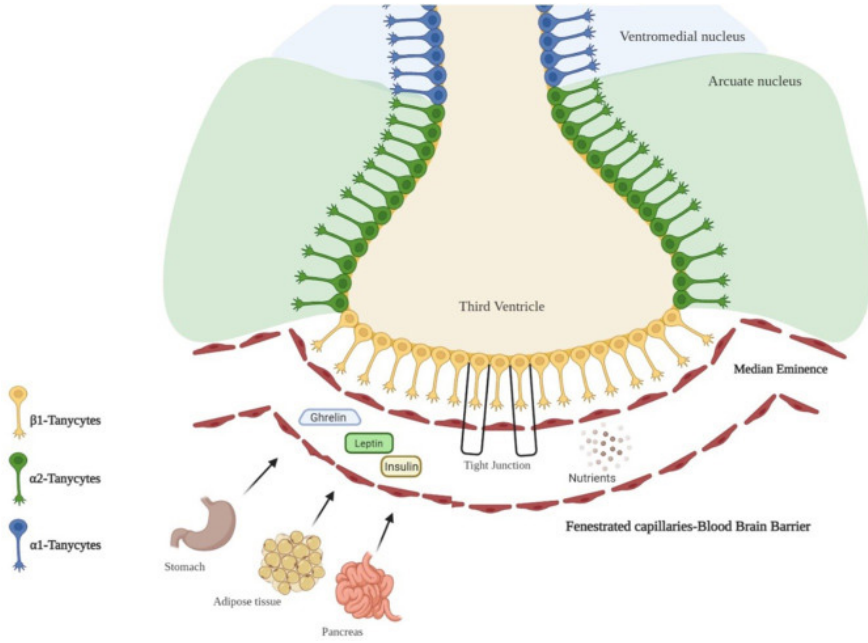

Figure 2. Interaction of the arcuate nucleus (ARC) region in the third ventricle region of the hypothalamus, the median eminence (ME), and the blood-brain barrier (BBB) (Vohra et al., 2022).

Five types of melanocortin receptors have been identified, namely MCR 1, MCR 2, MCR 3, MCR 4, and MCR 5 (Baldini and Phelan, 2019). Studies have shown that α-MSH acts as an agonist of the MC-4 receptor, and in human studies investigating the MC4 single-nucleotide polymorphism, such mutations are associated with increased appetite (Klockars et al., 2018). While melanocortin peptides that activate MC4 receptors also have an anorexigenic effect, the MC3/4 R antagonist induces obesity by showing orexigenic function. Leptin plays an active role in food intake and metabolism by regulating MC3R and MC4R activities in the melanocortin pathway. However, leptin and 5-HT receptors (5-HT1B, 5-HT2C) are expressed together in POMC neurons in the arcuate nucleus (Romano et al., 2018). Studies in which Leptin has been administered indicate that decreased POMC inhibition plays a role in reducing leptin nutrition (Vohra et al., 2022). When both human and animal studies in the literature are examined, it is stated that Leptin deficiency or LepRb gene mutations cause obesity and hyperphagia by affecting POMC expressions (Vohra et al., 2021).

Leptin, which can cross the BBB, binds to its receptor on POMC neurons and phosphorylates tyrosine residues (Tyr-1007, Tyr-1008, Tyr-985, Tyr-1077, Tyr-1138, Tyr-1141), which in turn leads to Janus-activated kinase (JAK2)- signal leads to the activation of transducer and activator of

transcription-3 (STAT-3) or PI3K-PDE3B-cAMP pathways (Fig 3). This then binds to the STAT-3 activator. JAK2 then phosphorylates STAT-3 to function as a transcription factor. As a result, dimerized STAT-3 is directed towards the nucleus to activate POMC and suppress AgRP, resulting in reduced food intake. However, with the activation of Tyr-985, the SH2 domain-containing phosphatase-2 (SHP-2) pathway is activated. This activation triggers the stages of protein growth factor receptor-bound protein-2 (GRB2) for downstream activation of RAS and mitogen-activated protein kinase (MAPK) and stimulates extracellular signal-regulated kinase (ERK). As a result, Leptin leads to dephosphorylation of STAT-3 protein via Tyr-985 via the SJP-2 pathway. In addition to this interaction, it has been shown that Leptin and insulin in POMC neurons mediate each other through a common signaling pathway to show anorexigenic properties. The pathway here is known to be via the activation of phosphoinositide 3-kinase (PI3K). (Baldini and Phelan, 2019; Cui et al., 2017; Klockars et al., 2018; Iwasa et al., 2022; Vohra et al., 2021).

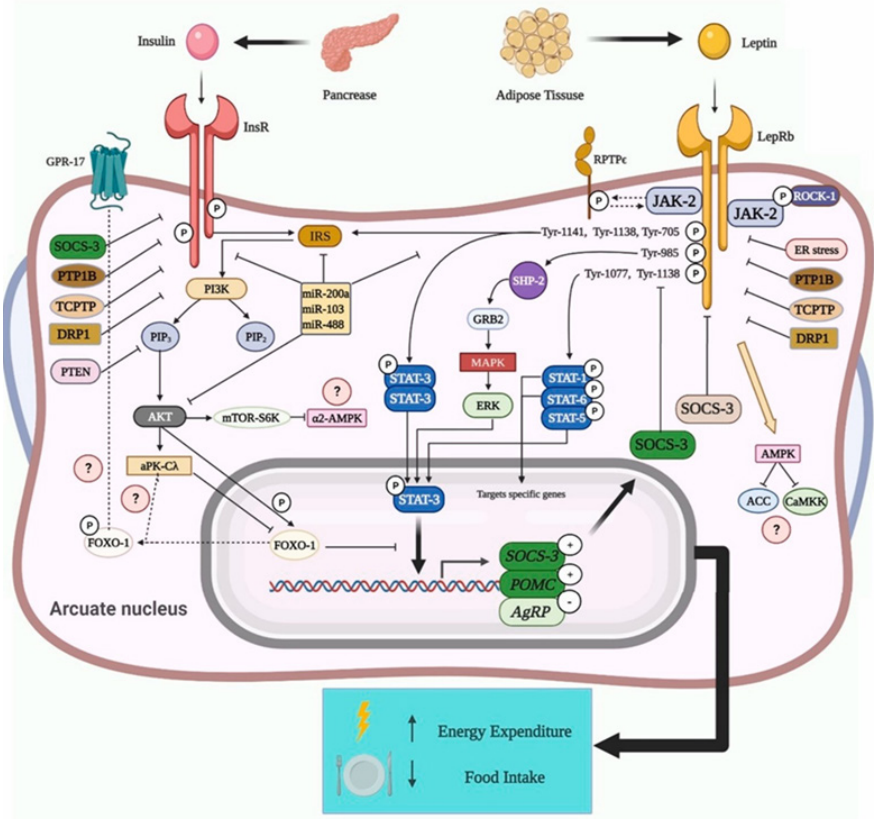

Figure. 3. Effects of Leptin and insulin in food intake on POMC neurons in the ARC (Vohra et al., 2021)

AgRP/NPY, Agouti-related peptide and neuropeptide Y; POMC, Pro-opiomelanocortin; BBB ,Blood-brain barrier; IP3, Inosito-1,4,5-triphosphate; CRE-B, cAMP response element binding-B; AMPK, AMP-activated protein kinase; ACC, Acetyl-CoA carboxylase; MCA, Malonyl-CoA; CPT-1a, Carnitine palmitoyltransferase-1a; FOXO-1, Forkhead box protein O-1; mTOR, Mammalian targets of rapamycin; TCPTP, T cell protein tyrosine phosphatase; JAK, Janus-activated kinase; STAT-3, Signal transducer and activator of transcription-3; LepRb, Leptin longest functional isoform receptor; SHP-2, SH2 domain-containing phosphatase-2; GRB-2, Growth factor receptor-bound protein-2; MARK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; SOCS-3, Suppressor of cytokine signalling-3; PTP1B, Protein tyrosine phosphatases-1B; PTEN, Phosphatase and tensin homolog; DRP1, Dynamin-related protein-1; InsR, Insulin receptor; IRS, Insulin receptor substrates.

The importance in the concept of the leptin-melanocortin pathway attributed to the dorsolateral (POMC/CART) pathway is the stimulation of leptin neurons in which melanocortins, one of the POMC gene products, are located. Because it is known that POMC and AgRP neurons are effective in the central regulation of the melanocortin system and this system is also responsible for providing energy balance. Many recent studies show co-expression of arcuate nucleus POMC and AgRP. When metabolism of leptin signal decreases, POMC gene expression decreases, and vice versa; AgRP expression increases when energy is increased or at normal leptin levels (Morano et al., 2021). It is accepted today that this regulation is one of the underlying mechanisms of obesity. Studies have shown that Ghrelin, a hormone that targets AgRP/NPY neurons in the ARC and is converted from pre-proghrelin to the PC enzyme, stimulates food intake when extra energy is used in energy balance (Vohra et al., 2021). Today, it is known that Ghrelin is a hormone that directly stimulates nutrition and inhibits vagal afferent signals that play an essential role in energy homeostasis and even reduces the anorexigenic effects of Leptin (Williams et al., 2020). When activated Ghrelin is acylated in ARC and binds to growth hormone secretagogue receptor-1α (GHSR-1α), various signals such as AMP activated protein kinase (AMPK), Ca2+/CaM-dependent protein kinase kinases (CaMKK) pathway, nicotinamide phosphoribosyl transferase (NAMPT) activate their pathways. However, the mechanisms underlying the interaction of these pathways have not yet been determined (Vohra et al., 2021).

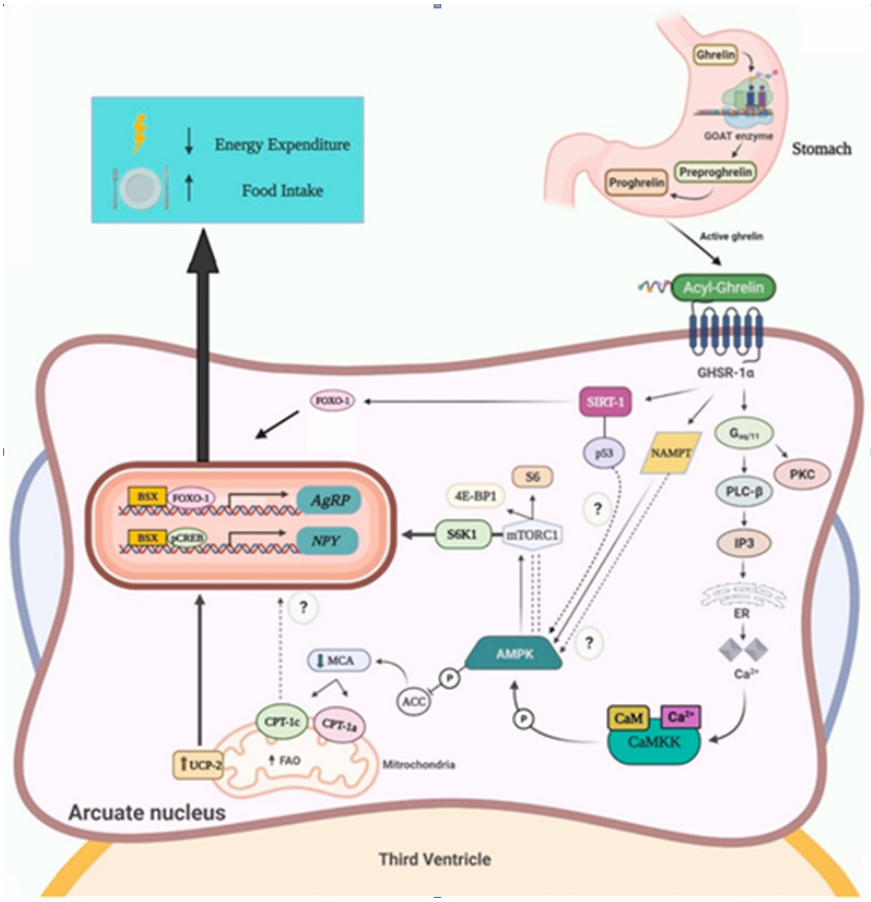

Figure 4. Effect of ghrelin on appetite in ARC neurons (Vohra et al., 2021).

ARC, Arcuate nucleus; AgRP/NPY, Agouti-related peptide and neuropeptide Y; PLC-β, PhospholipaseC-β; PKC, Protein kinase-C; IP3, Inosito-1,4,5- triphosphate; ER, Endoplasmic reticulum; CaM, Calmodulin; Ca2+/CaMKK, Ca2+/CaM-dependent protein kinase kinases; AMPK, AMP-activated protein kinase; FAO, Fatty acid oxidation; ACC, Acetyl-CoA carboxylase ; MCA Malonyl-CoA; CPT-1a, Carnitine palmitoyltransferase-1a; BSX, Brain specific homeobox; FOXO-1, Forkhead box protein O-1; mTOR , Mammalian targets of rapamycin; UCP-2, Uncoupling protein-2; NAMPT, Nicotinamide phosphoribosyltransferase.

Drugs used in the treatment of obesity act through appetite mechanisms. Drugs that act on the central nervous system used for appetite suppression and weight control (write the explanations in English, Betul) Phentermine / Topiramate combinations approved by international health authorities such as Food and Drug Administration (FDA), European Medicines Agency (EMA) and currently used, drugs such as Naltrexone / Bupropion, Liraglutide, Semaglutide, Lorcaserin , drugs such as

Rimonanbant, which were previously approved and withdrawn due to their side effects, and unapproved but promising drug molecules such as Amylin mimetic- Pramlintide, Combined GLP-1, Oxyntomodulin, and Peptide YY therapy, Ghrelin Vaccines and Antagonists, Neuropeptide Y Inhibitors, Setmelanotide (Tak and Lee, 2021).

In general terms, signals from the adipose tissue, the gastrointestinal tract, and the periphery cause anabolic or catabolic effects in the person's metabolism by affecting the arcuate, paraventricular, dorsomedial nuclei ventromedial nuclei, thus the connections in the hypothalamus (Vohra et al., 2022). Although many neurotransmitters, neuropeptides, hormones, and even related gene regions affect healthy behavior and, therefore, weight control, the tissue they affect are known, their functions in the brain are complex and have not yet been fully elucidated. Since the effects of the relevant neurotransmitters also vary according to the receptor diversity, the multiple inputs of other connections make it difficult to say whether they increase or decrease the net effect on the concept of appetite. Structural and characteristic differences between individuals, socioeconomic and sociocultural differences, mood changes also affect eating behaviors. Altogether, we can state that treating mechanisms managed by multifactorial variables such as obesity and eating disorders requires multidisciplinary approaches.

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CHAPTER 18

MINIMAL INVASIVE TREATMENT APPROACHES IN PEDIATRIC DENTISTRY

Arş. Gör. Büşra MUSLU DİNÇ[1],
Arş. Gör. Enes Mustafa AŞAR[2]

1 Selçuk University, Faculty of Dentistry, Department of Pediatric Dentistry
E-mail: dt.busramuslu@gmail.com
2 Selçuk University, Faculty of Dentistry, Department of Pediatric Dentistry
E-mail: enesmustafasar@gmail.com

MINIMAL INVASIVE TREATMENT APPROACHES IN PEDIATRIC DENTISTRY

The ideal "child-friendly" treatment for decidious teeth; It is known that it should be planned to keep the tooth in the mouth symptom-free until the natural fall out, without stressing the child, preserving the vitality of the tooth if possible. In recent years, the definition of "Minimal Invasive Dentistry (MID)" has emerged as a new approach in the treatment of carious teeth, thanks to the developments in adhesive dentistry and scientific advances that provide a better understanding of the caries mechanism. MID, a new evidence-based dentistry approach, was first introduced to the literature by Mount, then Dawson and Makinson. The term of minimally invasive dentistry describes operative restorative interventions that respect patient comfort and dental tissues (Dawson & Makinson, 1992). Contrary to what most physicians think, MID does not mean only opening minimal cavities. (Burke, 2008; McIntyre, 1994). Today, the scope of minimally invasive dentistry has expanded further and the concept of "Minimal Intervention Dentistry (MID)" has emerged.

This method is based on early caries diagnosis and risk determination, optimum caries preventive measures, minimum loss of material in the first intervention to caries, healing by reminalizing caries, and using a restorative material with good biological properties and fluoride release (Frencken et al., 2012). Among these methods; sono abrasion, air abrasion, non-restorative caries treatment (NRCT), chemomechanical caries removal methods, hall technique (HT) and atraumatic restorative treatment (ART) as the most common treatment option. (Black, 1945; Kidd, 2012).

MID's strategy;

- Early diagnosis of dental caries and determination of caries risk
- Treatments for remineralization of demineralized enamel and dentin
- Taking optimum caries prevention measures
- It can be summarized as the minimally invasive design of operative interventions (Frencken et al., 2012).

From another point of view, the transmission route of severe acute respiratory syndrome, which is called COVID-19 and has become a global threat by affecting many countries and thousands of people, is direct contact, droplet and possible aerosol transfers (Rothan & Byrareddy, 2020). Considering the high success rate of the biological approach in caries management, it is thought that it would be more rational and more reliable to use minimally invasive treatment methods that generate minimal or no aerosols (Burke et al., 2020).

1.Hall Technique

Dentist in Scotland, Dr. The Hall technique, which was defined by Hall and has been applied and developed for more than 15 years; is the restoration of teeth with stainless steel crowns (SSC) without the need for local anesthesia and tooth preparation (Nainar, 2012). It does not require local anesthesia and the use of hand tools, as it is done without removing the caries and tooth preparation is not done (Innes et al., 2006). With its non-invasive design, it can be accepted more easily by the patient, and it also reduces the rate of untreated primary teeth due to its long-lasting restoration (Hesse et al., 2016a; Ludwig et al., 2014). In a study, it was reported that the majority of both children and families were satisfied with the SSC application performed with the Hall technique, and this treatment option was considered acceptable in terms of pain and appearance (Page et al., 2014).

Indications;

1. In early caries lesions diagnosed on radiograph, in teeth without pulpal lesion, intraradicular pathology, and at the same time with intact dentin tissue between the caries lesion and the pulp,

2. In teeth with moderate occlusal caries, which cannot be well isolated and restored with adhesive restorative materials,

3. In Class 2 lesions with or without cavitation,

4. In Class 1 lesions that do not have cavitation and the patient does not accept conventional dental treatment methods or fissure sealant application,

5. Hall technique can be used in Class 1 lesions with cavitation and where the patient does not accept conventional dental treatment methods or partial caries removal (Manual, 2015).

6. It is said that the time spent in the chair decreases when the Hall technique is used. For this reason, Hall technique can be preferred in cases where there is difficulty in establishing cooperation with the child (Innes et al., 2007).

Contraindications;

1. Hall technique should not be applied in teeth where the pulp is clinically exposed (Manual, 2015).

2. The use of the Hall technique without pulpal treatment is contraindicated in the following conditions:

- Presence of buccal sinus

- Presence of interradicular pathology-dental abscess,

- Night pain, presence of "irreversible" pulpitis,

- Presence of non-physiological mobility in the tooth,

3. In the presence of caries involving the pulp or in the absence of sufficient intact dentin tissue between the carious lesion and the pulp when examined radiographically,

4. Presence of clinical or radiographic findings involving the pulp,

5. Presence of pulp polyps,

6. In teeth where the pulp is clinically exposed,

7. If the tooth cannot be restored with SSC,

8. If there is a large material loss in the tooth that cannot be treated with conventional methods,

9. In teeth that have become self-cleaning, restoration is unnecessary, and only follow-up will be sufficient,

10. In the presence of Class 1 and Class 2 lesions where isolation is easy and adhesive restorative materials can be used,

11. In cavitation-free teeth that can be treated with fissure sealants,

12. In decayed primary molar teeth, which do not require restoration because there is very little time left for the permanent tooth coming from underneath to erupt,

13. The use of the Hall technique is contraindicated if the patient's cooperation is insufficient to preserve the airway (Manual, 2015).

14. If the family and child are not satisfied with the aesthetic results of Hall crowns,

In a study on this subject, it was stated that families were not satisfied with the aesthetics of SSCs and this could cause a limitation in terms of the Hall technique (Hesse et al., 2016b).

15. It has been stated that the use of the Hall technique may not be appropriate in autistic children (Dean et al., 2011).

16. If the patient is at risk for bacterial endocarditis, conventional methods in which all carious tissue is removed should be preferred (Manual, 2015).

With the Hall technique, the tooth is isolated from environmental factors, which causes the carbohydrate provided by the host diet to be cut from the plaque and thus the plaque content to change. Cariogenic plaque

is more sensitive to environmental changes than non-cariogenic plaque. If environmental conditions are changed, the plaque may lose its cariogenic potential. If the caries is effectively isolated from the oral environment, the role of the plaque in caries changes significantly and becomes less cariogenic, stopping the progression of the caries lesion (Ricketts et al., 2006; Skucha-Nowak et al., 2015). Studies have shown that the caries lesion regresses radiologically and clinically with tertiary dentin formation after the isolation of the tooth (Schwendicke et al., 2013).

In a published retrospective study, high clinical success was reported in teeth restored with both the Hall technique and conventional SSC (Ludwig et al., 2014). In another study, NRCT (non-restorative caries treatment), Hall technique, and conventional technique were compared in terms of children's behaviors and pain perceptions during treatment. As a result of the study, 50% of the 52 children had a showed positive attitude from start to finish to Hall technique. This rate was found to be 35% for conventional methods and 42% for NRCT. (Santamaria et al., 2015).

2. Non-Restorative Caries Treatment (NRCT)

Non-restorative cavity control (NRCC) involves managing the carious lesion without removing the carious tissue and, in most cases, placing a restorative material. The microbial environment of the biofilm resulting from the presence of free carbohydrates causes an imbalance in the demineralization and remineralization of dental hard tissues, resulting in caries lesion. NRCC aims to prevent further demineralization and facilitate remineralization while controlling biofilm activity on the tooth and lesion surface. The rationale for this minimally invasive treatment technique is based on the current understanding that dental caries develops at the level of plaque biofilm and reduces treatment-related anxiety in young and special needs children.

This method, also called unrestored caries treatment, has led to a paradigm shift in the treatment of dental caries in children. This new method of treating carious lesions without removing carious tissue recognizes that carious lesion is a localized symptom of dental caries. Since dental caries occurs at the level of plaque biofilm, the purpose of the procedure is to manage the activity of the biofilm on the lesion surface and to stop the caries lesion. Teeth selected for NRCT should not be symptomatic of pulpal pathology. This minimally invasive method of managing carious lesions is particularly effective in treating primary teeth with clearable and potentially removable lesions (Kher & Rao, 2019).

Non-restored caries treatment (NRCT) is a 3-stage treatment option for root surface caries lesions, coronal surface lesions with cavitation, and dentin spaces in the structure of the primary tooth. The first stage is

the improvement of the patient's oral hygiene procedures and habits. The second step involves exposing the dentinal lesion so that it is accessible to the toothbrush. In the third stage, when active dentin caries lesion is diagnosed or the risk of recurrence of carious lesion activity increases, treatment is supported with 38% silver diamine fluoride (SDF) or 5% sodium fluoride (NaF) varnish. NRCT has advantages over traditional restorative therapy as it avoids the onset of stress and fear that often results from invasive restorative therapy. It prevents an empty or harmful cycle of repair in active carious lesions and raises people's awareness of their own responsibility for oral health and the quality of the oral hygiene procedure. NRCT is advocated as an important and effective treatment option, especially in pediatric dentistry, with patients or parents/caregivers who can accept responsibility for the disease and engage in dietary modification and regular brushing with fluoride toothpaste. It should not be used when urgent operative action is required, such as pain, infection, or sepsis, or when patients are not prepared to change the behaviors that led to caries development in the first place (van Strijp & van Loveren, 2018). Frequent follow-up to prevent pain and pulpal pathology is one of the basic principles of the NRCT treatment concept (Gruythuysen, 2010).

In a study, it was shown that 33% of the failure rates in the 9-44 month prospective clinical evaluation of NRCT were related to the patient. This result demonstrates that NRCT on oral hygiene requires a high level of patient and parent cooperation (Hansen & Nyvad, 2017).

Another study compared traditional restorative treatments with NRCT. Medium/large cavitations were followed up without restoration, brushing with fluoridated toothpaste was recommended, traditional restorative protocols were applied to the control group, and clinical results were reported to be similar in the experimental and control groups after three and a half years. In another part of this study, it was stated that well-applied non-restorative caries treatment had a positive effect on quality of life and all treatment protocols were effective in reducing pain, sleep problems, and aggression levels in children for a period of one year (Leal et al., 2013).

3. Atraumatic Restorative Treatment (ART)

"Atraumatic Restorative Treatment (ART)" is defined as a treatment which the dentist reaches the deprivation area and cleans the active soft parts of the caries with hand tools and closes the caries cavity with glass ionomer cement in the 1990s, when rotating instruments could not be used in poor countries due to technological impossibilities, and the transfer of the people of the region to the place where these opportunities would not take place for a long time (J. E. Frencken et al., 1996; Frencken et al., 1994).

The issue of developing a new, inexpensive, effective and easy

approach due to the inadequacy of dental treatment opportunities in economically lagging countries was brought to the agenda in 1992 at the meeting of the "7th South and West Africa International Dental Research Association" in Harare. In this meeting, it was reported that more than 90% of the teeth with caries lesions in Africa were left untreated until they became painful, and were extracted when they became symptomatic. It has been seen that extraction therapy is the basic treatment principle in underdeveloped countries (J. Frencken et al., 1996). In order to improve the current situation in these countries, the technology required for oral and dental health (suction and mobile tour equipment, etc.) brought from developed countries and used in limited areas was not sufficient to solve the problem. The main reasons for this are; power cuts, lack of adequately equipped health personnel, and difficulties encountered in transporting equipment from one region to another are shown. These experiences have brought up the ART treatment method, which can be applied by health personnel, in the field conditions, in which only hand tools are used without the need for extra equipment.

First, as part of the primary oral health program in Tanzania in the mid-1980s, caries was cleaned with only hand tools and then ART treatment was applied by closing it with CIS, an adhesive restorative material (Frencken & Holmgren, 1999).

Usage Areas of ART;

1. In the introduction of first dental treatment in very young children who have not met a dentist before,

2. In patients experiencing extreme fear or anxiety to the dental approach,

3. In patients with mental and/or physical disabilities,

4. In patients in need of care at home and in the elderly living in a nursing home,

5. ART can be used as a transitional treatment to stabilize conditions in the treatment of individuals at high caries risk (Pilot, 1999).

Compared to the pain that may occur due to the pressure and heat generated by the rotating instruments during conventional treatments, there are many studies reporting that it is more easily accepted by the patients due to the fact that only the decalcified tooth tissue is removed and the pain is less due to the absence of heat (de Menezes Abreu et al., 2009; Frencken & Holmgren, 1999; Gao et al., 2003; Lopez et al., 2005; Mickenautsch et al., 2007; Mickenautsch et al., 1999; Rahimtoola & van Amerongen, 2002; Schriks & Van Amerongen, 2003; van Amerongen & Rahimtoola, 1999;

Van Bochove & Van Amerongen, 2006).

The uncomfortable sound caused by rotating instruments is absent in ART. Thanks to this feature, it is a form of treatment that can be preferred in mentally retarded individuals, children and individuals with high dental anxiety.

ART, which has the opportunity to be applied outside of clinical conditions and only using hand tools; It is evaluated in pediatric dentistry and caries treatment programs that can be applied to large masses, due to its advantages such as not needing anesthesia, ease of application, not requiring special equipment or environment, low cost, and high patient acceptance (Horowitz, 1996; Tyas et al., 2000; Yip & Samaranayake, 1998).

Studies show that the high-viscosity CIS material used in class 1 ART restorations applied to primary and permanent teeth is successful. CISs with moderate viscosity are not recommended for use in ART (van't Hof et al., 2006).

ART Application Steps;

- Isolation of the tooth from saliva with cotton rolls
- Reaching the caries lesion with hand tools (Enamel Hatchet, Enamel Access Cutter)
- Removal of carious tissue with the help of an excavator
- Wiping the cavity (10% Polyacrylic acid, 10-15 seconds)
- Placement of high-viscosity GIC into the cavity (Press with Vaseline finger to allow excess GIC to overflow)
- The flood is in the form of GIC removal (Shen, 2003).

In summary, dental caries has become an important public health problem for children due to the high incidence of caries in children in the primary dentition period and the barriers to treatment such as limited cooperation. Failure to treat early childhood caries can have serious negative consequences. Conventional treatments are always an option; however, minimally invasive treatment methods seem very attractive for patients who meet the indication criteria, due to the increased time spent in the chair, the long-term success of the procedure being dependent on sensitive working conditions, and the need for more patient compliance.

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