NEW FRONTIERS IN HEALTH SCIENCES

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DUVAR

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Chapter 1

The Importance Of Assessing Motor Skill Development And Physical Fitness In Children

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INTRODUCTION

Many definitions have been made for movement, which is a sign of human vitality (Akkoyunlu, 1996). In general, motion can be defined as a change in body position or a change in a part of the body (Mengütay, 1999). Voluntary movements that serve a purpose or lead to a functional outcome are defined as motor skills (Newell, 2020). Gallahue and his colleagues (2019), define the term motor skill as the purposeful and learned movement task of the body and limbs.

Gallahue (1982) proposed the pyramid model, which demonstrates that motor development begins in the womb and continues in subsequent years, and with this model, he explained the stages of motor development. According to the model, the period consisting of two stages, the information gathering phase (in utero - 4 months) and the information decoding phase (4 months - 1 year), is defined as the reflex movement period. The period consisting of two stages, the stage where reflexes disappear (0-1 year) and the initial control stage (1-2 years), is defined as the period of primitive movements. The period of fundamental movements consists of three stages: the initial phase (2-3 years), the early phase (4-5 years), and the maturity phase (6-7 years). The stages described as the specialized phase (7-10 years), the general phase (11-13 years), and the specialization phase (14 years and above) constitute the period associated with sports-related movements. In this model, which illustrates the stages of motor development, development is limited to the childhood period. However, in later years, Gallahue and Ozmun (1995) developed the hourglass model, in which they examined the stages of lifelong motor development. In this model, sand, which is a living substance, is placed inside the hourglass. In this model, there are two separate bottles for environmental and genetic factors, and sand starts to enter the hourglass from both. The environmental bottle has no lid, but the genetic bottle has a lid, and the amount of sand in this bottle is constant.

In this context, the key point is that the sand, symbolizing the substance of life, is both a genetic and environmental product, rather than which bottle the hourglass is being filled from (Gallahue et al., 2019). In this model, the developmental stages show similarities to the pyramid model. However, there is a significant difference in the sports-related movement period. The hourglass model consists of three stages in the period of specialized movements: the transitional phase, the application phase, and the life-long use phase.

Motor development is an important factor in children's overall development, contributing to their ability to perform daily life skills. In this context, providing opportunities for a child to explore their surroundings and offering them space

throughout all stages of development is crucial. This allows the child to learn new skills and sets the foundation for them to use these skills throughout their lifetime.

FUNDAMENTAL CONCEPTS RELATED TO MOTOR DEVELOPMENT

Fundamental Motor Skills

Children move and engage in physical activity through the application of fundamental motor skills. Fundamental motor skills are considered the building blocks for advanced movements and sport-specific skills (Robinson and Goodway, 2009).

Fundamental motor skills are divided into two categories: locomotor and object control skills. Skills used to move the body from one place to another are called locomotor skills. Examples of these skills include running, jumping, hopping, and sliding. Object control skills (manipulative skills) are skills that involve using the hands and feet to perform actions such as throwing, catching, hitting, and kicking a ball (Haywood and Getchell, 2009). Fundamental motor skills are an important factor in motor development, contributing to children's future motor development and their ability to learn new skills (Goodway et al., 2010).

Gross Motor Skills

Gross motor skills are defined as skills that include locomotor movements, which require moving the body from one point to another, such as crawling, walking, running, and jumping. They also encompass non-locomotor movements, which are movements performed without the need to change position, such as sitting, kneeling, and standing. These skills also include movements that involve maintaining balance in the current body position (Turan ve Yükselen, 2015).

Fine motor skills

Fine motor skills are defined as the coordinated ability to perform tasks requiring hand-eye coordination, such as holding a pen, using scissors, or zipping up a zipper (Trawick-Smith, 2013).

Shape of Movement (Form)

It is defined as a model that emerges by arranging two or more movements in a sequence. The throwing action produced by coordinating the shoulders,

arms, torso, and leg movements when a child throws a tennis ball is referred to as "form" (Özer ve Özer, 2004).

Performance

The term performance used to report the result of a movement or action is the measurable feature of the movement and is generally expressed as distance or time duration (Özer ve Özer, 2004).

Physical Fitness

This can be expressed as the ability required for the completion of our daily tasks or for performing an activity at the desired level (Kaya, 2007).

Physical fitness encompasses elements related to skills and health. It is defined by the World Health Organization (WHO-1990) as the ability to successfully perform a muscular task and by the Centers for Disease Control and Prevention (CDC-1985) as the capability to engage in physical activity, either existing or acquired in the future, related to movement (Akın, 2003). The American Alliance for Health, Physical Education, Recreation, and Dance (AAHPERD) in 1980 stated that health-related physical fitness is an ongoing process from birth to death, determining the optimal performance in all aspects of life, from various levels of physical fitness affecting physical activity to limiting diseases and disorders.

Yanardağ (2001) states that health-related physical fitness consists of factors that enhance the body's functional capacity and includes components related to improving health such as muscular strength and endurance, body composition, cardiovascular endurance, flexibility, balance, and coordination. Performance-related physical fitness, on the other hand, encompasses factors that are important for an individual's performance skills, such as strength, speed, agility, and reaction time, particularly in demanding physical activities like sports. If there is inadequacy in any of these elements, it is referred to as a low level of physical fitness.

ASSESSMENT OF MOTOR SKILLS

The assessment of motor skills is important not only for typically developing children but also for identifying the specific needs of children with special requirements. Indeed, assessing motor skills in typically developing children can provide insights into areas where they may have weaknesses as well as highlight their strengths. Additionally, these assessments can offer valuable information about the developmental processes of infants and children at risk, enabling the implementation of early intervention programs. At this point, what

is crucial is considering the child's strengths and weaknesses before making assessments in the developmental deficiency group, without stigmatization.

Assessments can involve both formal and informal approaches. Formal approaches include motor proficiency tests, movement test batteries, and perceptual-motor tests. Informal assessments, on the other hand, encompass observation, surveys, family interviews, expert notes, and video recordings.

In this section, commonly used scales for the assessment of motor skills are often provided.

Test of Gross Motor Development (BükBÖT)

If deficiencies in gross motor skills development are not identified or corrected, a child may face long-term issues related to motor skills. Furthermore, deficiencies in gross motor skills that significantly impact a child's personality can also lead to secondary social problems. Therefore, assessing gross motor skill development should be an important aspect of early childhood monitoring programs (Tepeli, 2007).

The Gross Motor Skill Measurement Test (BüKBÖT)" is developed based on the "Test of Gross Motor Development - Second Edition (TGMD-2)," which was standardized according to American norm values by Dale A. Ulrich in 2000. It is an individually administered norm-referenced test designed to assess the gross motor functions of children aged 3-10. This test consists of 12 movement skills. Six skills measure running, galloping (running with long and easy strides), hopping on one foot, running and jumping over obstacles, long jumping, and sliding performance. The other six skills evaluate striking a stationary ball, dribbling a ball, catching a ball, kicking a ball with the foot, throwing a ball, and rolling a ball. It can help quickly identify motor skill deficiencies when compared to same-aged children's performance in basic motor patterns (Kanbir et al., 2021).

The Bruininks-Oseretsky Motor Proficiency Test-2 (BOT-2)

This test, which is an important tool for identifying existing or potential motor deficits (Bruininks and Bruininks, 1977), it was developed by Bruininks (1978) to measure the motor proficiency of children aged 4.5 to 14.5 years. BOMYT long form consists of 8 subtests and a total of 46 items. It is also a comprehensive indicator of motor proficiency and also measures both gross and fine motor skills. The Bruininks-Oseretsky Motor Proficiency Test was updated in 2005 and became the Bruininks-Oseretsky Test 2 (BOT2), consisting of 8 subtests and 14 items (Bruininks and Bruininks, 2005).

Peabody Motor Development Scale-2 (PDMS-2)

The scale was first developed by Folio and Fewel in 1983 (Folio and Fewell, 1983). Later, the scale was developed and became the Peabody Motor Development Scale-2. The scale, developed to determine the gross and fine motor development levels of children from birth to 71 months, can be used in children with healthy development and children with special needs. Gross motor sub-dimensions of the scale consists of 4 dimensions: reflexes, balance, displacement and object orientation. Fine motor dimensions consists of two dimensions: grasping and hand-eye coordination (Folio and Fewell, 2000).

Ankara Developmental Screening Inventory (AGTE)

Ankara Developmental Screening Inventory has been developed to evaluate the development of infants and children aged 0-6 with information obtained from mothers. Early diagnosis of babies and children who experience developmental delay or are at risk, through AGTE, allows timely precautions to be taken. The inventory includes items covering language-cognitive, fine motor, gross motor, social skills, and self-care domains. AGTE is administered by asking the child's parents, and they provide answers in a 'Yes-No-I don't know' format. It has been reported that obtaining information from both parents, especially regarding premature and at-risk children, yields healthier results (Savaşır, Sezgin and Erol, 1994).

Denver Developmental Screening Tests

The age range of 0-6 years is considered a critical period, and the Denver II test is one of the most commonly used tests during this period.

The test consists of 116 items grouped into four sections, which include personal-social development, fine motor development, language development, and gross motor development. It is used to identify potential developmental issues in seemingly healthy children.

This test is valuable in three fundamental areas:

- Screening seemingly healthy children for potential issues.
- Objectively identifying suspected functional deficits in developmental delay.
- Monitoring at-risk infants (e.g., those with prenatal issues, low birth weight or premature births, multiple pregnancies, a family history of developmental problems, babies born using assisted reproductive techniques, etc.) (Madan and Tekin, 2015).

Portage Early Childhood Education Program

Portage Early Childhood Education Program was developed in 1969 by Shearer and Shearer specifically for children with special needs aged 0-6 years old. The Portage program is a home-based instructional program that empowers families by providing them with information on what and how to teach their children, as well as how to observe their children's behaviors. It actively involves families in their children's educational programs (Shearer and Shearer, 1972).

The Portage program assesses six areas using a checklist: stimulation, self-care, motor development, social development, cognitive development, and language development (Birkan, 2002).

The Bayley Infant Development Scale

This scale is a product of the interaction of neurological processes maturing at different rates. When identifying motor problems, it is essential to start with the assessment of muscle tone, primary reflexes, and posture-related reflexes. The Bayley Scale is one of the commonly used and trusted developmental assessment tools for evaluating infant development. It consists of three scales that assess the development of infants between 2 months and 30 months of age in three areas: the Mental Scale, Motor Scale, and Infant Behavior Record Form (Özelli, 1978).

PHYSICAL FITNESS MEASUREMENT AND EVALUATION

General meaning of physical fitness is the ability to perform daily tasks with vigor and alertness, without excessive fatigue, and with enough energy reserves to handle unexpected or unforeseen situations during leisure activities (Tepeli, 2007).

Physical fitness, which includes elements related to both health and skill (Caspersen, Powell and Christenson, 1985), is assessed through tests that measure cardiovascular endurance, muscular strength and endurance, muscle power, speed, flexibility, agility, power, speed, and balance performances (Özer, 2001).

In addition to these tests, some specialized tests have been developed for measuring physical fitness. In this section, some of the frequently mentioned tests in the literature are included.

Brockport Physical Fitness Test

The Brockport Physical Fitness Test is a criterion-referenced test related to health. It was developed as a product of the "Project Target" study (1993-1998),

supported by the United States Department of Education's Office of Special Education and Rehabilitative Services and designed by the State University of New York. It is possible to create a customized test battery using the twenty-seven different tests included in the assessment, tailored to specific disabilities and age groups. Developed for children and adolescents aged 10-17 with and without disabilities, this test provides information about an individual's health-related physical fitness. It offers a wide range of options that can also be designed for individuals with intellectual disabilities, spinal cord injuries, stroke, congenital anomalies, amputations, or visual impairments (Bağdatli and Deliceoğlu, 2014).

Eurofit Test Battery

The "Eurofit Test Battery" was developed under the supervision of the European Council's Sport Development Committee with the aim of defining and assessing the existing abilities in children and young people. This research aimed to develop methods that could be used in research and in schools and clubs. The Eurofit Test Battery is designed to determine physical fitness, physiological function, and motor performance in school-age youth aged 6-18 (Şenel, 1995).

The Eurofit Test Battery is a set of tests used to assess an individual's level of physical fitness by measuring various motor skills such as flexibility, strength, balance, speed, and more. It is employed to determine at what level an individual possesses these physical abilities (Uygun, 2019).

The Eurofit Test Battery, developed and widely accepted through numerous international studies and research, is used as a measurement tool in various research and studies for the purpose of determining, defining, and evaluating the physical fitness levels of children and individuals (Yılmaz, 2020).

Münich Physical Fitness Test

The Münich Physical Fitness Test (MFT) is a valid and reliable test used in schools in Germany to assess physical fitness in children and adolescents aged 6-18. This test allows for objective scoring and interpretation of motor performance, as well as peer comparisons based on age and gender. It consists of six parameters: ball bouncing, target shooting, forward bending, vertical jumping, hanging, and a step test (Bös and Titlbach, 2002).

RESULTS

Early childhood spans the period from 0 to 8 years of age in human life, and children acquire fundamental knowledge and skills in various developmental

domains during this time, which they will use throughout their lives. The importance of this stage in human life is emphasized through various studies, underscoring the need to support children's development in the early childhood years through accurate and appropriate means (Tunçeli and Zembat, 2017).

Ulutaş and colleagues (2017) emphasize that motor development is open to improvement during the preschool period, and during this time, children can benefit from various programs and activities that can support their overall development, particularly in enhancing motor skills.

Physical fitness components are necessary for performing daily life activities, participating in physical activities, and demonstrating motor skills such as walking, running, jumping, hopping, skipping, catching, and throwing adequately (Özer, 2001; Tamer, 2001).

Deficiencies in motor development can stem from shortcomings in other developmental areas, as well as from inadequacies in physical fitness (Bağdatlı and Deliceoğlu, 2014). As a result of all these deficiencies, children may lag behind their peers. In this context, many studies have compared typically developing children with children with special needs in terms of motor development and physical fitness parameters.

Ilhan and Esentürk (2015), conducted a comparative examination of certain physical fitness parameters between children with intellectual disabilities and typically developing peers. The findings of the study, when compared with the literature, suggest that children with intellectual disabilities tend to lag behind their typically developing peers in physical fitness, possibly due to having fewer opportunities to participate in physical activities and exercises.

Demirci and Demirci (2016) assessed the gross and fine motor skills of children with specific learning difficulties. According to the research results, they encountered challenges in developing gross and fine motor skills, delayed hand preference, and difficulties in playing with toys such as puzzles, blocks, and Lego.

In another study that assessed typically developing children and intellectually disabled children in terms of physical fitness parameters, it was reported that intellectually disabled children tend to have lower levels of physical fitness compared to typically developing children. This is primarily attributed to their initially lower levels of physical activity and various contributing factors, which is a common finding in research in this field (İlhan and Esentürk, 2015).

In another study conducted on the development of early childhood special education, it was reported that the practices in our country are not at the desired level (Pınar, 2006). The statement emphasizes the need for prevention of

disabilities, early identification of children with disabilities, comprehensive assessment of children, and subsequently providing early education services to both children and their families, highlighting that the current state in these areas is insufficient. Early diagnosis and intervention can support a child's development and enable them to realize their full potential. In this context, it is recommended that typically developing children should undergo developmental assessments at specific intervals during their lives, including once between 0-6 months, between 12-18 months, between 2-3 years, and between 5-6 years (Madan and Tekin, 2015). Assessing children's motor development with appropriate and reliable measurement tools in the early stages is essential for identifying potential issues, creating necessary educational programs for deficiencies, and providing optimal support for their development (Su and Taşkıran, 2022).

As a result of this study, it is recommended that parents consult with experts and have the relevant assessments conducted to ensure that children can continue their healthy development and that children with special needs do not lag behind their peers. The motor development and physical fitness tests examined in this study provide information about children's development. Motor assessment tests will serve as a guide for families and professionals. At the same time, applying early intervention programs according to test results can enable children with special needs to start education early. In this context, it is crucial to emphasize the importance of early assessment and intervention to support children's motor development and physical fitness, ensuring that all children, including those with special needs, have the opportunity to reach their full potential and thrive in their development.

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Chapter 2

Evaluation of Gases Affecting Air Quality in Animal Shelters

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INTRODUCTION

The air quality of shelters is very important in terms of animal welfare. Distribution and direct characteristics of gases found in air analyses of shelters. Some types of these gases found in the shelter have positive effects on healing, while others have negative effects. In this section, a general evaluation of the gases in the air conditions in animal shelters is made.

Animal production also involves the people who raise livestock and the external environment. This effect can be experienced by people directly or indirectly by influencing it. In animal shelters, there are many gases produced by both animals and the environment. Various ambient air distributions of these gases can be increased to specific levels due to insufficient distribution.

Weather conditions in animal shelters have many effects on animal and human health and well-being. Studies show that animals exposed to diseases and gaseous diseases in animal shelters may develop acute or chronic respiratory diseases (Alberta Government, 2023).

In shelters, there may be gases that naturally affect the humanity of animals, as well as unwanted gases and substances in other places, consisting of biological, physical, and chemical formations. These unwanted gases and disturbances cause the air to decrease in shelters. The reasons for the release of these airborne gases are generally animal metabolism, fertilizer, and resource breakdown, regardless of external weather conditions. These gas rates vary depending on factors such as the type of shelter, animal species, animal growth, ration given, fertilezer management, ventilation, air temperature, and humidity level (Uğuz, 2023).

Type of shelter;

An important factor affecting gas emissions in the environment is the design of animal shelters (Gerber et al., 2013). Shelter types in livestock farming have varied greatly from past to present with technology. In the past, the main structure of most shelters was made of materials such as stone, soil, clay, or brick, but today these materials are replaced by more modern materials such as cement, brick, gas concrete, etc. It is observed that the products are preferred. In addition, it is seen that today, country governments support larger and more spacious shelters where animal welfare is more taken into account and direct breeders in this direction.

In modern livestock shelters, the indoor air quality must be suitable for the health of workers and animals (Choinière and Munroe, 1993). However, modernity has affected the insulation in some buildings so much that the air-flow inside the shelter has come to a standstill. This situation caused gases to

move away through windows, roofs, and doors in old-style shelters, but in modern ones, the gases could not move away easily (Göncü et al., 2015). In addition, the concrete material in the shelters tends to prevent the accumulated gases from being easily discharged (Hayvan Refah ve Konforu, 2023).

Animal species;

When the effects of gases in shelters are evaluated in terms of animal species, it is observed that some animal species affect the environment more than others. It can be said that, as a species, cattle breeding species cause more gas emissions individually than the species in the sheep and poultry sector. However, upbringing style greatly affects the release of these gases. For example, gases generated from production in the poultry sector are higher than other animal production due to intensive animal use and some physiological reasons. Especially in pig production buildings, there are often high concentrations of NH_3 and CO_2, it has been reported by some researchers that these negatively affect the health of both animals and humans (Ulens et al., 2014; Xu et al., 2016). Additionally, it has been determined that monogastric animals emit less CH_4 than ruminants (Jensen, 1996).

Animal's age;

As animals get older, their body structures naturally both grow and develop. Growth and development are physiological characteristics that are important in animal breeding. Growth and development are generally expressed as the weight increase of the living being and the differentiation in body structure (Akçapınar and Özbeyaz, 2021). As a result of this situation, many of the natural physiological needs of animals increase with age. As a result of these increasing physiological needs, the rate of gases and other factors affecting air quality released into the environment increases with this growth.

Ration;

The effect of animal rations on air quality is generally twofold. The first is directly related to the ration itself, and the second is related to the consumption of the ration by the animal.

Under the immediate direct influence of the ration; Harmful gases may be released during the preparation and storage of rations in animal shelters. Many of these harmful gases may occur as a result of the activities of microorganisms in manure, silos, and rotting feed (Ergül, 1989).

If the ration is consumed by the animal; Total CH4 emissions per animal per day can vary greatly depending on the forage/concentrate ratio of the diet, the

level of feed intake, the degree of fat inclusion in the diet, the digestibility of carbohydrates in the diet and the presence of any feed additives that may alter this (Johnson et al., 1995).

Ration has a significant effect on the nitrogen excretion pathway in ruminants. In their study, Powell and Broderick (2011) stated that reducing the protein rate in the feed ration is an effective method for reducing ammonia emissions from fertilizers applied to the field by reducing the mineralization rate of nitrogen in the obtained fertilizer. In other studies, it has been reported that it is effective in reducing the amount of crude protein taken with feed and protein broken down in the rumen, urea excretion, ammonia concentration, and N_2O from fertilizer (Külling et al., 2001, Lee et al., 2012, Luo et al., 2010).

Fertilizer management.;

When the manure in animal shelters is not stored properly, it causes environmental pollution both inside and outside the shelter. It is necessary to know the odor that manure emits into the shelter air and the harmful substances in the air and to ensure proper manure management to prevent harm to animals and people.

Generally, systems in which manure is stored for a long time cause more NH_3 and CH_4 production than systems in which it is removed from the environment daily. Therefore, manure management systems and shelter design greatly affect the spread of ammonia from animal production (Gerber et al., 2013).

It is said that the most important source of ammonia gas in shelter air is animal waste (Çayır, 2010). Apart from ammonia, it has been reported that gases such as sulfur compounds, methane, and carbon dioxide significantly affect air quality, and the main source of these gases is manure, urine, litter, feed, and wastewater (Hayvan Refah ve Konforu, 2023).

Air Conditioning;

Closed shelters for animal breeding must have adequate ventilation systems and fresh air intake must be provided. Heat, humidity, and ventilation are interrelated issues. With ventilation, humidity and temperature are balanced, and harmful gases are removed (Hayvan Refah ve Konforu, 2023).

Natural ventilation in the shelter is aimed at constantly removing polluted air, harmful gases, moisture, and microorganisms and providing fresh air into the shelter instead. Reasons such as lack of energy consumption, noiseless operation, and resistance to low air temperatures generally lead to natural ventilation in cattle and sheep shelters. However, in poultry farms with high

animal density, natural ventilation may be insufficient, and therefore mechanical ventilation is more commonly used in such shelters (Zou et al., 2020).

Temperature;

When the shelter environment is warm, it retains more moisture than the cold environment, and when adequate ventilation is not provided, more pollination occurs with high humidity. With a good ventilation system, the temperature of the shelter can be controlled and the relative humidity can be maintained. While temperature increases and excess humidity create an unhealthy environment for animals, they have a corrosive effect on building materials. Due to the effect of moisture on building materials, the life of the building is reduced (Yaylı and Kılıç, 2021).

When the air temperature level is between +16 and +18, breathing is normal, blood vessels are narrowed, sweat cells are inactive and there is heat balance. However, at -15 and +10 levels, feed consumption and body movements increase to increase heat production. If the environmental temperature is between +18 and +30, blood circulation in the body accelerates and blood vessels expand for heat loss (Akçapınar and Özbeyaz, 2021).

Temperature at undesirable levels causes stress in animals and an increase in body temperature, as well as a slowdown in the animal's movements (Dahl et al., 2020).

Shelter temperature directly affects the amount of gas in the manure, and as the temperature increases, the level of gas released from the manure increases. While it is recommended that the temperature inside the shelter should not exceed 14 °C and the humidity should not exceed 65% to ensure that the CO2 concentration inside the shelter does not exceed 3300 ppm and NH3 does not exceed 20 ppm, it is reported that the temperature in traditional and modern shelters should not exceed 17 °C and the humidity should not exceed 75%. As the temperature and humidity inside the shelter increase, the amount of oxygen decreases and the amount of carbon dioxide increases, thus making it difficult for the animals in the shelter to breathe (Bayhan, 1996).

Humidity;

Humidity formation in animal shelters can be caused by both environmental and animal sources. While there are many environmental reasons such as upbringing style, climate, and shelter type, the humidity level in the shelter may change due to animal factors such as sweating, urination, or breathing. For example, moisture is released into the air as a result of the animal's breathing,

and the humidity level may increase if the shelter is not adequately ventilated. As a result, this excessive level of humidity accumulated in the environment can not only harm animals but also cause materials in the environment to get wet and ammonia gas to combine with moisture to form ammonium hydroxide (Hayvan Refah ve Konforu, 2023).

It is stated that a relative humidity rate between 40-60% is suitable for pets, and a humidity level of less than 35% and more than 70% is not desired (Akçapınar and Özbeyaz, 2021). Some researchers generally want the humidity rate in animal shelters to be at least 50-60% (Demir, 2022).

Some animals that cannot sweat increase their breathing rate to maintain heat balance in the body. That's why the humidity level in some animal shelters is becoming more important. As the humidity increases, the amount of ammonia in the shelter also increases and animals may suffocate due to difficulty breathing. In addition, undesirable levels of humidity make feed and bedding wet and moldy, thus creating a suitable environment for the growth of some undesirable microorganisms. On the contrary, low amounts of humidity can cause excessive dust in the shelter and some undesirable irritations in the respiratory tract of animals (Demir, 2022).

Other factors;

When we look at other factors affecting gas concentrations in animal shelters; We can list many factors related to the animal itself, the breeder, natüre, or the environment. Each of these factors are topic that needs to be examined in detail. However, in this section, some gases that are found to be effective in evaluating the air quality in animal shelters, both naturally occurring in nature and formed in the shelter due to animal and other reasons, have been evaluated.

2. Gases

Within the scope of this research, ammonia, methane, hydrogen sulfide, carbon dioxide, carbon monoxide, and oxygen gases, among the most notable gases found in shelters, were evaluated.

2.1. Ammonia (NH_3)

Ammonia found in animal shelters is a product formed as a result of microbial decomposition of organic nitrogen compounds in feces. Nitrogen in feces is formed as urea in mammals and uric acid in poultry. Urea and uric acid rapidly break down to form ammonia and are released into the environment

shortly after excretion (Oenema et al., 2001). Gaseous ammonia has a significant irritating effect on the respiratory system (Costa et al., 2003).

Ammonia is a lighter gas than air and can be easily removed from the environment by ventilation. If humans are exposed to ammonia in amounts higher than 25 ppm, respiratory problems and skin and eye irritation may occur (Government of Alberta, 2023). Thanks to its characteristic strong odor, it can be easily detected even when its density reaches 5-10 ppm (Choinière and Munroe, 1993).

Ammonia is the main pollutant source of poultry houses and, when in high amounts, can negatively affect the health and welfare of the animal by reducing feed and weight gain (Seedorf and Hartung, 1999; Kristensen et al., 2000; Popescu et al., 2010; Barrasa et al., 2012).

When ammonia gas levels exceed 20 ppm in broiler chickens, the time to reach sexual maturity increases and the development rate decreases. Additionally, when the ammonia level in the shelter exceeds 50 ppm, ammonia inflammation occurs in chickens. In calves, it has been observed that when the ammonia threshold exceeds 50 ppm, their appetite decreases and their eyes become irritated (Bodur, 2023). Some researchers have stated that the NH3 rate in shelter air should not exceed 0.03% (Mutaf and Sönmez, 1984).

2.2. Methane (CH_4)

Methane is a compound with the chemical formula CH_4 (Carbon and 4 Hydrogen atoms). Methane is an element that can be found in many different sources. Natural methane can be found both underground and under the seabed. Methane, which is a gas at normal temperatures and pressures, has an odorless structure. Methane, which is found in many places, is produced in animals during the anaerobic fermentation of carbohydrates in the rumen. Animal feces, in particular, is an important source of methane because it contains cellulose that is broken down by methane-producing bacteria (Maurer et al., 2017; Mama and Seid, 2019).

When methane emissions are considered in terms of livestock; It is stated that CH_4 emissions are more common in closed-type enterprises where dairy farming or cattle breeding is carried out. In other words, ruminants produce more methane than other species such as pigs and poultry. Cattle not used for dairy production are the largest contributor to CH4 emissions from enteric fermentation, accounting for 51.8% of the total, followed by dairy cattle, buffalo, goats, sheep, and pigs (Zhang and Chan, 2014)). Methane emissions may also vary between animals of the same age and in the herd, depending on feed quality and intake (Philippe and Nicks, 2015; Rotz, 2018).

Methane in animal shelters does not normally pose a health hazard, but undesirable explosions may occur in shelters due to gas compression or ignition (Choinière and Munroe, 1993).

While the tolerance of animals to methane gas is 10,000 ppm, deaths can occur when it increases to 50,000 ppm (Bodur, 2023).

2.3. Hidrogen Sülfide (H_2S)

Hydrogen sulfide is formed as a result of microbial reduction of sulfate in water and microbial degradation of organic substances in feces (Xue et al., 1998).

Hydrogen sulfide is a poisonous gas that is heavier than air and soluble in water and can cause health problems if its concentration becomes too high. Hydrogen sulfide in animal shelters is found in barn troughs, underground, outdoor storage tanks, or unventilated areas such as a soil manure storage facility (Government of Alberta, 2023).

Hydrogen sulfide is the most dangerous gas produced by feces and its smell can be easily felt even at very low temperatures. The substance that generally gives the feces a bad smell is hydrogen sulfide gas. Because it overwhelms the sense of smell in high concentrations, workers cannot smell it, and as a result, it can affect the lungs and cause death (Choinière and Munroe, 1993). Hydrogen sulfide can be lethal to animals at high concentrations, and the target organ it affects is generally the central nervous system (Donham, 2000).

Some researchers (Bodur, 2023) state that there is an average of 2.18 ppm (0.0017%) of hydrogen sulfide gas in the air by volume, and the limit value of hydrogen sulfide is 20 ppm (0.016%) for cattle and sheep, and 10 ppm (0.008%) for chickens. They stated that '. Some researchers have stated that the H2S rate in shelter air should not exceed 0.001% (Mutaf and Sönmez, 1984).

It is known as a production problem, especially in pig breeding, where serious problems occur in terms of hydrogen sulfide (Kandylis, 1984). Although there are various reports in the literature about H_2S concentrations originating from pig houses, there is a lack of information about H_2S release from pig houses (Ni et al., 2000).

2.3. Carbon dioxide (CO_2)

Carbon dioxide is a compound consisting of one carbon and two oxygen atoms and generally exists in gaseous form. In animal husbandry, CO2 is a major problem when animal production is extremely intensive, meaning that too many animals share and breathe in an enclosed space. When high gas concentrations are reached, it can have adverse effects on animal health and

welfare. It is desired to keep the CO2 concentration below 3,000 ppm. This value is an important level for both animal welfare and quality meat production (Ni et al., 2012; Xie et al., 2017; Constantino et al., 2020). Some researchers have stated that the CO2 rate in shelter air should not exceed 0.35% (Mutaf and Sönmez, 1984).

Carbon dioxide and water are the primary by products of respiration. Every living animal produces carbon dioxide, and if there is too much carbon dioxide in the shelter, it can be a potential health hazard. Generally, in terms of animal husbandry, high levels of carbon dioxide are observed in poultry shelters during the winter months (Choinière and Munroe, 1993).

Carbon dioxide production of animals varies depending on the animal's species, body weight, and nutrition (Pedersen et al., 2008; Jeppsson, 2000). Because carbon dioxide is a heavier gas than air, it tends to stratify downwards. While the acceptable CO_2 level in animal shelters is desired to be below 3000 ppm (Guizzardi et al., 2006), this rate can reach up to 6000 ppm in winter (Ni et al., 2020).

Some researchers (Bodur, 2023) say that C02 value; They stated that it should not exceed 1,000 ppm for poultry houses, 10,000 ppm for pig breeding, and 3,000 ppm for cattle breeding.

While high concentrations of $C0_2$ cause dizziness and loss of consciousness in animals, very high concentrations can even cause death by suffocation (Buoio, 2023).

2.4. Carbon monoxide (CO)

Carbon monoxide is an odorless, colorless gas whose weight is close to the weight of air, so its presence cannot be detected. The reasons for the emission of carbon monoxide into the atmosphere are fossil fuel, exhaust gas, fire, and cigarette smoke in closed areas. The presence of this gas in high amounts in the air can cause dizziness, slowed reflexes, and even death (Aydınlar et al., 2009). Carbon monoxide, which has a poisonous effect, emits some carbon monoxide gas with cigarettes smoked inside the shelter and fire lit. When the concentration of this gas increases to 50 ppm, harmful effects are observed in animals (Alagöz et al., 1996).

2.5. Oxygen (O_2)

Oxygen is a gas that gives life to all living things on Earth. The oxygen in the shelter must be at certain levels. When the oxygen need of animals is examined, research has found animals (sponges) that remain alive even at a level between 0.5-4.0% compared to today's atmospheric pressure (Mills et al.,

2014). However, the situation is slightly different for pets living in shelters. Ventilation of shelters affects the air quality inside the shelter, affecting respiratory diseases and the comfort and productivity of the animal by increasing the amount of oxygen (O_2) taken in by breathing. When the oxygen level drops below 11%, breathing difficulties occur, and when it drops below 7%, it can cause death (Mutaf and Sönmez, 1984). Animals with the same metabolic rate need the same amount of oxygen per unit body mass, larger animals have slower metabolisms than smaller ones (which is also why they need less food per unit body mass). For example; 10 calves weighing 500 kg use more oxygen than one cow weighing 500 kg.

Gas Levels in Shelters by Animal Species

Gas levels in shelters may vary depending on animal species. Some animal species have higher levels of some gases than others. However, harmful gases such as carbon monoxide (CO), hydrogen sulfide (H_2S), and hydrogen cyanide (HCN), which are considered chemical asphyxiants, were not observed in most studies.

Gases and dust that are not removed from the shelter environment have negative effects on the health of calves and young animals. The dust formed in the shelter also increases the effect of gases on animals. While dust irritates the respiratory tract mucous membranes, it also causes permanent damage to the lungs and supports the growth of microorganisms. For this reason, it is important to keep dust formation at minimum levels in shelters.

In this section, gas values in the shelters of cattle, horses, poultry, sheep, swine, and some laboratory animals were examined.

3.1. Cattle

The gas values determined by some researchers in cattle breeding in shelters according to the type of rearing are shown in Table 1.

Table 1: Gas Values Detected in Cattle Shelters

Gases	Values	References
NH_3	7.4 (ppm)	Şahanoğlu and Koçak, (2014)
	0.13 (kg)	Leytem et al., (2011)
	9.0 (g)	Ngwabie et al., (2009)
	5.34 (kg)	Maasikmets et al., (2015)
	0-3.0 (ppm)	Jovović et al., (2019)
	2.100-3.000 (mg)	Koerkamp et al., (1998)
	1.5 (ppm)	Zhao et al., (2007)
	0.49 (kg)	Leytem et al., (2011)
CH_4	84.0 (kg)	Chianese et al., (2009)
	13.0 (g)	Ngwabie et al., (2009)
	87.13 (ppm-yaz ayları)	Snell et al., (2003)
	19.36 (g)	Maasikmets et al., (2015)
H_2S	11 (ppb)	Zhao et al., (2007)
	1049.7 (ppm)	Şahanoğlu and Koçak, (2014)
CO_2	1430-1700 (ppm)	Brose et al., (1998)
	1697-2281 (ppm)	Jungbluth et al., (2001)
	390-1690 (ppm)	Jovović et al., (2019)
	365 (ppm)	Zhao et al., (2007)

The maximum gas values stated by some researchers for cattle shelters are shown in Table 2.

Table 2: Maximum Acceptable Gas Values in Cattle Shelters

Gases	Values	References
NH_3	<10 ppm	European Food Safety Authority, 2009
CH_4	<10.000 ppm	Bodur, (2023)
H_2S	<0.5 ppm	European Food Safety Authority, 2009
	<% 0.016	(Bodur, 2023)
CO_2	<2.000 ppm	European Food Safety Authority, 2009
	<3.000 ppm	(Bodur, 2023)
CO	<50 ppm	(Bodur, 2023)

3.2. Horse

The values on the gases detected in some shelters reported by researchers in horse breeding are shown in Table 3.

Table 3: Gas Values Detected in Horse Shelters

Gases	Values	References
NH_3	0-7.0 (ppm)	Saastamoinen et al., (2015)
	0.7 (ppm)	Topczewska ve Rogowska, (2017)
CH_4	0 (ppm)	Saastamoinen et al., (2015)
H_2S	0 (ppm)	Saastamoinen et al., (2015)
	0 (ppm)	Topczewska ve Rogowska, (2017)
CO_2	500-700 (ppm)	Saastamoinen et al., (2015)
	530-980 (ppm)	Topczewska and Rogowska, (2017)

Maximum acceptable gas level values for horse shelters are shown in Table 4.

Table 4: Maximum Gas Level Values in Horse Shelters

Gases	Values	References
NH_3	<10 ppm	Elfman et al., (2011)
CH_4	<10.000 ppm	Bodur, (2023)
H_2S	<% 0.016	(Bodur, 2023)
CO_2	<3.000 ppm	Elfman et al., (2011)
CO	<50 ppm	(Bodur, 2023)

3.3. Poultry

The data on the gases detected by researchers in some shelters in poultry farming are shown in Table 5.

Table 5: Gas Values Detected in Poultry Houses

Gases	Values	References
NH_3	115.7 (mg), (layer)	Alberdi et al., (2016)
	0.16-0.06 (kg) (layer)	Fabbri et al., (2007)
	0.24 (kg-yaz ayları), (broiler)	Cheng et al., (2011)
	0.42 (kg-yaz ayları), (layer)	
	0.15 (kg-kış ayları), (broiler)	
	0.19 (kg-kış ayları), (layer)	
	5.8-28.5 (ppm), (broiler)	Redwine et al., (2002)
	0.23-10.77 (mg), (broiler)	Mihina et al., (2012)
	7.800 (mg), (layer)	Koerkamp et al., (1998)
	10.000-15.000 (mg), (broiler)	
CH_4	3.4 (mg) (layer)	Alberdi et al., (2016)
	0.02-0.08 (kg), (layer)	Fabbri et al., (2007)
	46.59-134.12 (mg), (broiler)	Mihina et al., (2012)
CO_2	1.984 (mg) (layer)	Alberdi et al., (2016)
	51.37-77.49 (kg) (layer)	Fabbri et al., (2007)

The maximum gas values stated by some researchers for poultry houses are shown in Table 6.

Table 6: Maximum Acceptable Gas Values in Poultry Houses

Gases	Values	References
NH_3	<20 ppm	Bodur, (2023)
CH_4	1.000-5.000 ppm	Choiniere and Munroe, (1993); Esmay and Dixon, (1986)
H_2S	<% 0.008	(Bodur, 2023)
CO_2	5.000-30.000 ppm (86 USA)	Choiniere and Munroe, (1997)
	<1.000 ppm	(Bodur, 2023)
CO	35-400 ppm (86/87 USA)	Choiniere and Munroe, (1993); Esmay and Dixon, (1986)
	<50 ppm	(Bodur, 2023)

3.4. Sheep

The data on the gases detected in some shelters according to the type of sheep breeding are shown in Table 7.

Table 7: Gas Values Detected in Sheep Shelters

Gases	Values	References
NH_3	4.14-18.32 (ppm)	Uzal and İlhan, (2019)
	5 (kg)	Kiliç et al., (2021)
	0.77-15 (ppm)	Kiliç et al., (2017)
CH_4	0 (ppm)	Uzal and İlhan, (2019)
	18 (kg)	Kiliç et al., (2021)
H_2S	0 (ppm)	Uzal and İlhan, (2019)
CO_2	794,7-1553,3 (ppm)	Uzal and İlhan, (2019)
	457-1022 ppm	Kiliç et al., (2017)

The maximum gas values stated by some researchers for sheep shelters are shown in Table 8.

Table 8: Maximum Acceptable Gas Values in Sheep Shelters

Gases	Values	References
NH_3	<60 ppm	Kılıç, 2013
CH_4	<10.000 ppm	(Bodur, 2023)
H_2S	<% 0.016	(Bodur, 2023)
CO_2	<3.000 ppm	(Bodur, 2023)
CO	<50 ppm	Okuroğlu, (1987)
	<50 ppm	(Bodur, 2023)

3.4. Swine

The data on the gases detected by some researchers in swine breeding shelters are shown in Table 11.

Table 11: Gas Values Detected in Pig Shelters

Gases	Values	References
NH_3	54.0-147.0 (g)	Heber et al., (2000)
	2.000-4.500 (mg)	Koerkamp et al., (1998)
	22.7 (g)	Dong et al., (2009)
	34 (ppm)	Donham and Pendorf, (1985)
	2.64-22.9 (mg)	Mihina et al., (2012)
	33.51-189.63 (mg)	Mihina et al., (2012)
CH_4	975.36-9948.78 (mg)	Mihina et al., (2012)
	6.7 (g)	Dong et al., (2009)
	1.4 (ppm)	Donham and Pendorf, (1985)
H_2S	19.6 and 146 (ppb)	Thorne et al., (2009)
	0.03 (g)	Dong et al., (2009)
CO_2	1640 (ppm)	Donham and Pendorf, (1985)
	9.1 (ppm)	Donham and Pendorf, (1985)

The maximum gas values that should be in pig shelters are stated in Table 12.

Table 12: Maximum Acceptable Gas Values in Pig Shelters

Gases	Values	References
NH_3	10-20 ppm	Buoio et al., 2023
CH_4	<10.000 ppm	(Bodur, 2023)
H_2S	<% 0.016	(Bodur, 2023)
CO_2	5.000-30.000 ppm (86 USA)	Choiniere and Munroe, 1997
	<10.000	(Bodur, 2023)
CO	<50 ppm	(Bodur, 2023)

3.4. Laboratory animals

The air exchange rate within laboratory animal facilities should be such that clean, fresh air is provided to all animals and personnel at all times. Due to the research conducted on laboratory animals and their cage structures, the values of these animal shelters and the environment where the animals are located are at very different levels.

Inside the cage temperature, humidity, and ammonia levels are generally higher than room levels. The main components of concern for air quality in laboratory animal facilities are ammonia, carbon dioxide, particulates, and volatile organic compounds. Defects resulting from chronic ammonia exposure in rats are seen both live and postmortem. Although it has been suggested that maximum ammonia levels in cages should be 50 ppm (Allmann-Iselin, 2000), data from other rodent species indicate that exposure to ammonia levels of 25 ppm over 7-days causes lesions in the nasal passages. This situation suggests that the ammonia level is very high (Ferrecchia et al., 2014; Mexas et al., 2015). Maintaining acceptable air quality can generally be achieved through the frequency of cage changes and, in the case of individually ventilated cages, appropriate air exchange at the cage level (Canadian Council on Animal Care, 2023'a).

Housing conditions in laboratory animal breeding vary slightly due to cage and experiment construction stages. Table 13 shows the values examined for a laboratory animal and also for rabbits bred.

Table 13*:* Gas Values Detected in Rabbit Breeding

Gases	Values	References
NH_3	14.3 (mg)	Calvet et al., (2011)
	1,64 (ppm)	Ooms et al., (2008)
	7.0 (g), (damızlık), 4.3 (g), (besilik)	Calvet et al., (2011)
CO_2	7.041 (mg)	Calvet et al., (2011)
	517,8 (ppm)	Ooms et al., (2008)

The maximum gas and particle values that should be in laboratory animal shelters are shown in Table 14.

Tablo 14: Maximum Acceptable Gas and Particle Values in Laboratory Animal Shelters

Gases	Supply air target value	Target value	Maximum value	References
NH_3	0 ppm	<5 ppm	<25 ppm	Canadian Council on Animal Care, (2023b)
CO_2	350-600 ppm	<500 ppm	<5.000 ppm	
Particulates	<28.2 milyon/m^3	<35.3 milyon/m^3	<176.5 milyon/m^3	
Toplam uçucu organik bileşikler	0 ppb	<200 ppb	<1 ppm	
CO	-	-	<50 ppm	(Bodur, 2023)

CONCLUSION

Many effects affect the air quality in animal shelters. These effects can be caused by both animals and the environment. Air quality in shelters also varies greatly depending on the type of animals. While some animal species have a high tolerance to undesirable gases in the air, some have lower levels.

It has been observed that it is appropriate for pets to have the dust density in the shelter at a minimum level, the temperature inside the shelter to be between 14-16 C°, and the relative humidity to be between 40-60%. In addition, there must be an adequate ventilation system to ensure fresh air intake. The frequency of cleaning of bedding should be evaluated according to the animal type.

When gas levels in shelters are generally evaluated; It is thought that H2S and CO are the most undesirable gases in shelters, that NH3 should be 10 ppm, CO2 should be 2,000 ppm, and CH4 should be below 10,000 ppm, which would be suitable for most animal species.

As a result, suitable shelter structures for each animal housed in shelters should be built carefully and thoroughly researched. Because the air quality in shelters affects both the animals and the breeders working there in terms of welfare and health.

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Chapter 3

Geriatric Polypharmacy and Nursing Management

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INTRODUCTION

Advancements in the healthcare sector worldwide, coupled with a decrease in birth and death rates due to improved living standards and well-being, have led to an increase in average life expectancy. As a general notion, individuals aged 65 and older are now considered "elderly," with those between 65 and 74 classified as "young elderly" and those aged 75 and above as "late elderly" (Orimo et al., 2006). A similar trend is observed in Turkey, where the elderly population is rapidly increasing, currently constituting 8% of the country's population. Furthermore, due to improvements in healthcare and quality of life, life expectancy at birth in Turkey is 75.3 years for males and 80.3 years for females (Kaya & Gamsızkan, 2022).

With the aging process, a decline in organ reserves and physiological deterioration in the functionality of many organs are observed. The rate and degree of this functional decline can vary among individuals and within the same individual over time (Navaratnarajah, 2017). It is essential for elderly individuals to maintain their quality of life and lead an active life as part of the community during this period. The need for up-to-date and accurate data for planning healthcare services for the elderly has increased, given that a range of age-related health issues (e.g., diabetes, coronary artery disease, cerebrovascular events, osteoporosis, degenerative joint diseases) may necessitate rehabilitation and advances in the diagnosis and treatment of chronic diseases, thereby extending the aging period for the elderly. As the prevalence of chronic diseases increases, elderly individuals are increasingly using multiple medications (Güç, 1997; Arslan et al., 2000).

The rising prevalence of geriatric syndromes and chronic illnesses, along with the potential for multiple prescriptions from different physicians for elderly individuals with multiple conditions, and the risk of polypharmacy due to age-related changes in drug pharmacokinetics and pharmacodynamics leading to potential side effects, underscores the importance of rational drug use. This situation contributes to increased morbidity and mortality, reduces quality of life, and raises healthcare costs. Therefore, clinical approaches focused on rational drug use should be adopted to address this issue and improve the quality of life for elderly patients (Bahat et al., 2020; geriatri.org, 2022).

Geriatric Polypharmacy

The term polypharmacy originates from the combination of two Greek words, where "poly" means multiple, and "pharmacon" is derived from the word "pharmacon," meaning drugs. Polypharmacy, although subject to various definitions, generally involves the daily use of 4-5 or more medications, using

more drugs than clinical indications warrant, and at least one unnecessary drug (Hilmer et al., 2007; Tanrıöver, 2017). It holds particular significance in cases where multiple diseases coexist. Polypharmacy is defined as the concurrent use of five or more medications and is considered a key determinant of inappropriate prescriptions in elderly individuals. This term encompasses unnecessary, incorrect, and omitted prescriptions (Zullo et al., 2018).

It is estimated that 35% of elderly patients using multiple medications in primary healthcare services develop some side effects, with 48.2% of these side effects associated with drug use, and 59.1% of them being preventable (Ministerio et al., 2008). There are several reasons for polypharmacy in the elderly, including an increase in the number of comorbidities, multiple prescriptions, prescription cascades, inadequate physician knowledge regarding side effects and drug interactions, and patient and caregiver-related factors. Polypharmacy can lead to consequences such as drug side effects, drug interactions, treatment non-adherence, increased costs, hip fractures, weight loss, falls, cognitive impairment, prolonged hospital stays, and mortality (Bozkurt et al., 2019). However, with proper treatment approaches and monitoring of side effects, it can be highly effective in the treatment of multiple diseases in elderly individuals. Nevertheless, polypharmacy can lead to a decrease in quality of life, increased healthcare expenditures, and reduced patient compliance (Secoli, 2010).

Multimorbidity is defined as the coexistence of two or more chronic health problems in the same individual and is commonly prevalent in the elderly population (Salive, 2013). The presence of multiple chronic conditions simultaneously increases the complexity of treatment management for both healthcare professionals and patients, potentially negatively affecting health outcomes. Multimorbidity is associated with adverse effects such as a decrease in quality of life, worsening assessed health status, decreased mobility, increased hospitalizations, physiological stress, increased healthcare resource utilization, as well as increased mortality and costs (Masnoon et al., 2017). This is because one or more medications may be used to treat each condition (Maher et al., 2014). Medications commonly used in the daily lives of elderly patients, including antihypertensives, lipid-lowering drugs, antidepressants, antiplatelets, antidiabetics, non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, caffeine, fruit juices, non-pharmacological agents, and herbal preparations, carry a potential risk for drug interactions. Therefore, drug interactions are a significant concern for elderly patients, and consideration of drugs that could potentially interact during prescription is essential during treatment (Tunca, 2006).

The Concept of Rational Drug Use

The pharmaceutical industry is a constantly evolving field, characterized by increased dynamism through the introduction of new drugs. The accessibility of prescription and over-the-counter medications, coupled with the proliferation of drug quantities, has raised questions about how drugs should be effectively utilized and has brought forth the concept of rational drug use (RDU) (Beggi and Aşık, 2019). Inappropriate use of medications is a common public health concern. Rational drug use was first defined by the World Health Organization (WHO) during a meeting held in Nairobi in 1985 as "the use of medications that meet the clinical needs of patients, in doses that meet their individual requirements, for an adequate period, and at the lowest cost to them and their community." Any situation that does not conform to this definition is considered irrational drug use (IDU) (WHO, 2022). Another definition of rational drug use entails a systematic approach that involves the accurate diagnosis of the patient's medical condition, the selection of drugs appropriate for the indication, the determination of the correct dosage, administration form, and duration, all while considering economic factors (Macit et al., 2019). According to the estimates of the World Health Organization, more than 50% of medications are prescribed, dispensed, or sold inappropriately, and half of all patients do not use their medications correctly. Misuse and overuse of medications, including in Turkey, is a significant public health issue (titck.gov.tr).

With the increasing importance of artificial intelligence in the healthcare sector, its integration into healthcare has extended to areas such as dosage form design and drug discovery (Raza et al., 2022). In the healthcare sector, artificial intelligence serves critical functions such as reminding patients of important information and providing medication support (Taş, 2022). When elderly individuals forget their medication dosages, it is advisable to consider the use of medication reminder applications, taking into account factors such as whether they understand the side effects of their medications, when to seek medical attention for side effects, the purpose and duration of use of recommended medications, and whether they have previously used these medications (Elkin, 2020).

In Turkey, a common issue related to rational drug use is the practice of obtaining medication without consulting a doctor. Research indicates that 52.6% of elderly individuals obtain medication from doctors, 21.1% based on their own request, 13.2% from recommendations by friends, 7.9% from pharmacists, and 5.2% based on suggestions from neighbors (Arslan et al., 2000; Yeşil et al., 2012). Another national study conducted by the Ministry of

Health in 2018 revealed that nearly half of patients tended to use over-the-counter medications, and 37.4% used medications from home when they fell ill. Additionally, more than half of the participants believed that antibiotics did not cure every illness. Therefore, continuous education and emphasis on the importance of rational drug use are essential for individuals and families. Furthermore, healthcare professionals should receive ongoing training on rational drug use, and healthcare institutions should establish standards and policies to guide healthcare professionals in this regard (Bakımlı, 2023).

Nursing Management

Nurses take a pioneering role in the management of chronic health conditions. There are numerous Nurses play a pioneering role in the management of chronic health conditions. There are numerous ways in which nurses and other healthcare professionals can contribute to reducing the number of prescribed medications (Erbay, 2018). Considering the biophysical, psychological, social, and cultural factors of elderly individuals, nurses have significant roles and responsibilities in medication management. Ethical and legal responsibilities of the nurses involved in this process are also of paramount importance (Kaya et al., 2018). Every nurse should possess knowledge about the disease, its clinical features, and clinical management (Demirağ and Hintistan, 2020).

Nurses have various opportunities to facilitate medication reduction processes aimed at minimizing polypharmacy. Being knowledgeable about polypharmacy, understanding its associated adverse outcomes, and comprehending specific guidelines for medication reduction can assist nurses in effective communication with healthcare providers. Nurses often act as mediators or coordinators among various healthcare providers and, in this role, can ensure patients' medication safety (Kim and Parish, 2021). Nurses evaluate all aspects to ensure that patients receive individualized and cost-effective care, and they have competence in reducing the use of potentially inappropriate medications (PIMs), particularly. They can promote non-pharmacological strategies to prevent the use of specific medications, such as sedatives or laxatives. By utilizing evidence-based non-pharmacological approaches, nurses can prevent the use of specific medications to treat common symptoms like sleep disturbances, constipation, and behavioral symptoms of dementia (Kim and Parish, 2021).

Preventing Geriatric Polypharmacy

There are standardized evidence-based tools available to guide healthcare providers in making pharmacological decisions that meet the needs of elderly adults. Some tools, such as the Beers Criteria, Screening Tool of Older Persons' Prescriptions (STOPP), and Screening Tool to Alert doctors to Right Treatment (START) criteria, provide medication freedom (Fick et al., 2003; O'Mahony et al., 2015).

The Beers Criteria initially emerged as a guide listing potential inappropriate medications for elderly individuals, first described in 1991. This list includes medications that may not be appropriate for elderly adults, especially those with specific conditions or syndromes like heart failure, and takes into account potential drug interactions that may occur in the elderly (Fick et al., 2003).

The STOPP/START criteria, on the other hand, provide clinicians with a list that helps them consider which medications should not be used or discontinued, much like the Beers Criteria. It also includes a list of medications that may provide better outcomes for elderly adults and can be used as a checklist when compared to the Beers Criteria (O'Mahony et al., 2015).

Medication tapering refers to the deliberate process of reducing medication dosages or discontinuing medications. This process is not only used for polypharmacy situations but also when patients need to discontinue potentially harmful medications or realize that a medication is no longer effective. While the importance of medication tapering was introduced to the medical literature as early as 2003, it has been emphasized more in recent years (Skinner, 2015).

Patient-centered communication is a critical factor at the heart of a successful polypharmacy reduction strategy. However, patients and their families may not fully understand the specific benefits and risks of each medication. Therefore, adequately informing patients is highly important. Elderly adults often use multiple medications and can make medication adjustments, making it crucial to ensure correct medication use (Cross et al., 2020).

Based on these strategies, nurses are considered to play a crucial role in preventing and managing polypharmacy in geriatric individuals. This allows nurses to lead initiatives that guide the healthcare team and patients in improving medication management practices.

Literature

Cheng et al. (2023) present a meta-synthesis of qualitative studies aiming to examine the perceptions and experiences of nurses providing care to elderly adults with polypharmacy. In this research, a total of nine studies were

reviewed, involving 91 nurses in total. The analysis results reveal four main themes, including the challenges faced by elderly adults with polypharmacy, the importance of multidisciplinary teams, caregiving roles for elderly adults, and the complexity and barriers of polypharmacy management.

Another systematic review and meta-analysis study conducted by Rankin et al. (2018) aimed to identify interventions that enhance medication appropriateness to prevent polypharmacy and hyperpolypharmacy in elderly individuals. These interventions were compared, and the results did not show a consistent intervention effect or difference in medication-related issues among the studies.

Bhagavathula et al. (2022) conducted a study aiming to report the prevalence of polypharmacy/hyperpolypharmacy in elderly adults with Parkinson's disease and explore the relationship between polypharmacy and the disease. The study's results indicate a significant relationship between polypharmacy and Parkinson's disease, as well as a strong association between hyperpolypharmacy and Parkinson's disease.

McKracken et al. (2017) carried out a study in hospitals treating hypertension and diabetes to describe the prevalence of polypharmacy and determine potential relationships between polypharmacy and lower variable markers for treated hypertension and diabetes. Research findings showed that patients with polypharmacy were more likely to receive diagnoses of hypertension or heart failure, and those with complex hypertension treatment were also more likely to experience polypharmacy. Additionally, patients with complex diabetes treatment were found to receive more non-diabetic medications compared to those with higher HbA1c levels.

O'Dwyer et al. (2016) conducted research in Ireland to assess the prevalence of polypharmacy (5-9 medications) and hyperpolypharmacy (10+ medications) and identify associated demographic and clinical characteristics in an aging population with intellectual disabilities. According to the study's results, 90% of participants reported medication use, with a 31.5% prevalence of polypharmacy and a 20.1% prevalence of hyperpolypharmacy.

Kurczewska-Michalak et al. (2021) presented an article exploring methods for preventing geriatric polypharmacy. Among the interventions described in this analysis, the most recommended ones include various types of medication reviews based on implicit or explicit criteria. Implicit criteria-based approaches are not prominently highlighted due to their rare usage and limited applicability. Most publications advocate the use of explicit criteria such as STOPP/START, Beers criteria, and Medication Appropriateness Index. However, these criteria

may have limited applicability because they potentially include long lists of inappropriate medications.

Çelikçi (2021) assessed polypharmacy and inappropriate medication use in elderly patients in a palliative care service according to the Beers and TIME-to-STOP criteria. It was observed that 47% of patients in the polypharmacy group had polypharmacy. The potential inappropriate medication rate was found to be 8.3% according to the Beers criteria and 11.7% according to the TIME-to-STOP criteria. This study, focusing on a group of elderly, frail patients, revealed that polypharmacy could contribute to potential inappropriate medication use.

Datlı Yakaryılmaz and Eraydın (2022) aimed to evaluate the relationship between polypharmacy and malnutrition in patients with type 2 diabetes in their study. The existing findings indicate that polypharmacy is quite common in elderly patients with type 2 diabetes and is often associated with malnutrition.

Sofulu and Karadakovan (2022) conducted a study to determine the knowledge and practices of geriatric individuals regarding polypharmacy and medication use. The study revealed that the knowledge level of geriatric individuals regarding medication use was insufficient. It was found that 59.3% of individuals did not know the names of the medications they were taking, 68.3% had no knowledge of how medications interacted with food and beverages, 64.2% occasionally forgot to take their medication, 20.3% did not pay attention to the medication's expiration date, and 74.8% experienced side effects related to medication use.

Bozkurt et al. (2019) investigated both the presence of inappropriate medication use and the existence of polypharmacy in hospitalized patients aged 65 and older, as well as the impact of these inappropriate conditions on the length of their hospital stay. When examining the presence of inappropriate medication use in the patients, it was found that 59.4% of patients, or 77 individuals, had inappropriate medication use. Among these medications, "theophylline" was the most commonly used inappropriate medication, with a rate of 33.3%.

Öztürk and Uğraş (2017) conducted a study to evaluate medication use in patients aged 65 and older and to provide information about polypharmacy. The study revealed that the most common chronic diseases were hypertension (48.1%), coronary artery disease (27.0%), diabetes mellitus (23.2%), respiratory diseases (17.2%), and hyperlipidemia (12.8%). Multiple medication use was observed in elderly patients. While 17.8% of patients did not use medication regularly, 10.5% used one medication, 13.7% used two medications, 11.3% used three medications, 8.7% used four medications, and 38% used five or more medications concurrently. Symptomatic treatment was very common, and one

out of every two patients used proton pump inhibitors or nonsteroidal anti-inflammatory drugs.

CONCLUSIONS

As a result, an increase in the number of chronic health problems and the number of medications used for their treatment is observed with the aging process. This situation leads to a problem called geriatric polypharmacy. Polypharmacy is a common issue in elderly individuals and can have negative effects on health outcomes. The research discussed in this article examines the relationships between polypharmacy and elderly patients and various strategies for managing this problem. Various methods are suggested for preventing and managing geriatric polypharmacy. Firstly, rational drug use in geriatric individuals should be encouraged, and patients should be educated about their medications. Nurses play an important role in this process and can implement various strategies to improve medication management for patients. Managing the issue of polypharmacy in elderly individuals is a complex process that requires collaboration and awareness among healthcare providers, patients, and families. Effectively addressing this problem can improve the quality of life for elderly individuals and reduce healthcare costs.

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Chapter 4

Inflammation and Anti-Inflammatory Drugs

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INFLAMMATION

Although inflammation can be defined very simply as localized leukocyte accumulation, it is actually a complex defence mechanism created by various endogenous and exogenous stimuli in vascularised tissues. Inflammation is a strong and exaggerated physiological response that occurs at the cellular and humoral level in the organism against tissue damage caused by infectious, physical, chemical and other factors. It is also known that inflammation affects platelets. Inflammation was first discovered in A.D. It was described by Celsus, who lived in the 1st century, as redness, increased temperature, pain and swelling; Later, loss of function was also added to these features (Dunne 1990, Higgins 1985). The purpose of such a reactive response is to eliminate the damaging agent and the resulting products and to enable the repair and renewal of the damaged tissue after providing control by keeping the pest confined to its location. (Ustaçelebi 1999, Arthur et al. 2001, Tahiroglu and Kara 2022). Although there are many classifications regarding inflammations, the accepted classification is the one based on the duration of the inflammatory process. According to this classification, inflammation is divided into two: acute and chronic (Dunne 1990, Bullock 1996).

Acut Inflammation

Acute inflammation is short-lived, lasting from a few minutes to a few days. Acute inflammation is characterized by exudation (vascular) and leukocyte accumulation (cellular) (Maslinsk et al. 1998, Karadurmuş 2003). In the acute inflammatory process, blood vessels form the center of the reaction. There are three basic components of acute inflammation. a) Change in vascular diameter (vasodilation), increase in blood flow (congestion-stasis). b) Structural changes in the microvascular area, increased permeability. (Brattsand 1982). c) Collection of leukocytes in the injured tissue by passing through the endothelium (Malaya 2003). In the earliest phase of inflammation, very short-term reflex vasoconstriction occurs (Moncada et al. 1973). Following this, vasodilation occurs in the arterioles, capillary beds and venules (Moncada et al. 1973, Rao et al. 1994, Ogonowski et al. 1997). Increased vasodilation increases regional blood flow and increases intravascular hydrostatic pressure. This pressure rise causes stasis. As a result of stasis, protein-rich fluid passes into the extravascular tissue, creating edema (Bratsand 1982, Bullock 1996). This fluid, which accumulates in the tissue space as a result of stasis, not only dilutes toxic and irritating substances accumulated in that area, but also plays an important role in transporting leukocyte and complement factors (Dunne 1990, Bullock 1996). They migrate towards the periphery and come face to face with the

vascular endothelium. In the second stage, called adhesion force, leukocytes adhere tightly to the endothelium. In the migration phase, leukocytes migrate out of the endothelium to the damaged area with the help of chemotactic agents (Di Rosa and Sorrentino 1968, Meade et al. 1986, Dunne 1990, Bullock 1996). Leukocytes exit the vascular lumen into the extravascular space, kill microorganisms in the damaged area, break down necrotic tissues and foreign antigens, and release chemical mediators and oxygen radicals, causing tissue damage (Dunne 1990, Dawson et al. 1991, Cuzzocrea et al. 1997). While this dominance of leukocytes lasts for the first 6-24 hours, this situation turns in favor of monocytes in the following 24-48 hours (Imhof and Dunon 1997).

Chronic Inflammation

Chronic inflammation is considered a long-term inflammation in which active inflammation and healing processes occur together (Arthur et al.2001). Chronic inflammation is considered a long-term inflammation in which active inflammation and healing processes occur together. In some types of injury, the response to the damaging agent is chronic inflammation from the beginning. Although the damaging factors that cause chronic inflammation are less toxic than those that cause acute inflammation, a deficiency in healing processes can cause longer-lasting injury. Fibrosis is a common feature of many chronic inflammatory diseases and is an important cause of organ dysfunction. Chronic inflammation; persistent infections (Mielke et al. 1997, Co et al. 2004, Clare et al. 2003). It may occur during long-term exposure to potentially toxic agents and autoimmune diseases. Chronic inflammation occurs with the formation of proliferative cells. These are macrophages, lymphocytes and plasma cells (Dunne 1990, Arrigoni 1988). Macrophages are a component of the mononuclear phagocytic system, which consists of circulating monocytes and tissue macrophages composed of bone marrow-derived cells. The half-life of monocytes in the blood is approximately 1 day (Carlos et al. 1993). When monocytes reach extravascular tissue, they undergo a transformation and form larger phagocytic cells called macrophages (Maurer et al. 2002, Rosenberger and Finlay 2003,). Macrophages also have the ability to be activated (Risco et al.1995, Tsuji et al.2003). When they are activated, the size of the cell and the lysosomal enzyme content increase. Its metabolism becomes more active. Their ability to kill the organisms they phagocytose and some tumor cells is revealed. Signals activating macrophages; It consists of cytokines (especially IFN-γ) released from sensitized T lymphocytes, bacterial endotoxins, various mediators formed during acute inflammation, and extracellular matrix proteins such as fibronectin. Activated macrophages secrete numerous biologically active

products (Vervoordeldonk 2002, Trowbridge 1990, Kaur and Halliwell 1994). These; They are cytokines, eicosanoids, reactive oxygen products, neutral proteases, complement components and coagulation factors. These mediators create tissue destruction, angiogenesis and fibrosis, which are characteristic features of chronic inflammation. In acute inflammation, macrophages die in areas where the irritating substance is cleared and healed, and they enter the lymphatics and are eliminated from the body. However, macrophage accumulation in the focus of chronic inflammation is permanent. Continuous secretion of lymphocyte-derived factors is an important mechanism that ensures the accumulation or immobilization of macrophages in the inflammatory focus. IL-4 or IFN-γ also stimulate macrophages, causing these cells to fuse and form large, multinucleated cells called giant cells. Under appropriate conditions, macrophages also have the capacity to proliferate. Other cell types that play a role in chronic inflammation; lymphocytes and plasma cells (Trowbridge 1990). Lymphocytes are mobilized in any immune reaction, as well as in non-immune inflammation. T lymphocytes are in a reciprocal relationship with macrophages in chronic inflammation. Plasma cells are formed as a result of B lymphocyte activation. They create antibodies against antigens in the area of inflammation or against changing tissue components. Eosinophils characteristically play a role in immune reactions mediated by immunoglobulin E (IgE), such as around parasitic infections or in allergies. Granulomatous inflammation is a distinct pattern of chronic inflammation. It is characterized by clusters of activated macrophages with an appearance similar to enlarged squamous epithelial cells. Granulomas are seen in relatively few pathological conditions, especially tuberculosis. Therefore, recognizing the granulomatous pattern is important to identify a limited number of diseases, some of which are life-threatening. Granulomas can also form due to foreign bodies that are difficult to break down and are called foreign body granulomas. Granulomas may occur against some organisms (Listeria, Salmonella) to which T cells respond immunologically or against indigestible particles (Mielke et al.1997, Co et al.2004, Clare et al. 2003,). In these cases, cytokines secreted from activated T lymphocytes enable macrophages to transform into epithelioid cells or giant cells (Dominic et al.2004). Granulomas may also occur in autoimmune diseases such as sarcoidosis, Wegener's granulomatosis, and Crohn's disease (Gepdiremen et al.2004). Interestingly, granuloma formation is also seen in some malignancies such as Hodgkin and non-Hodgkin lymphoma (Ramprasath et al.2004). To put it briefly, granuloma protects the organism against chronic infection (Co et al.2004).

ANTI-INFLAMMATORY DRUGS

The main drugs used in the treatment of pain and inflammation are steroidal anti-inflammatory drugs (NSAIDs) and non-steroidal anti-inflammatory drugs (non-steroidal anti-inflammatory drugs; NSAIDs) (Sinom and Mills 1980, Jürgen 2000,). NSAIDs are the most commonly prescribed drugs after antibiotics. The prevalence of NSAID use in society is calculated as 5% (Hasçelik 2002). In addition to the anti-inflammatory drugs mentioned above, penicillamine, colchicine, quinine derivatives, gold compounds and some plants with proven anti-inflammatory effects (etc: gossypin) are also used in inflammatory events (Abu-Shakra et al. 1998, Perez 2001, Borstad et al. 2004, Rethy and Balo-Banga 2004, Yildiz et al. 2021).

Steroidal Anti-Inflammatory Drugs

Steroidal anti-inflammatory drugs produce a more significant anti-inflammatory effect than NSAIDs (Masferrer et al. 1994). These effects are probably; It depends on lysosomal membrane stabilization, decrease in capillary permeability, prevention of migration of leukocytes to the area of inflammation, inhibition of phagocytosis of damaged cells (especially decrease in T lymphocyte production) and release of IL-1 from leukocytes. Cortisol; It suppresses the synthesis of iNOS, COX and phospholipase A2 (Vane 1976, Sakurai and Sawamura 2003). It inhibits phospholipase A2 activity indirectly by increasing the release of lipocortin, a known inhibitory protein (Wallner et al. 1986, Vane and Botting 1987, Flower et al. 1994). Phospholipase A2 inhibition also inhibits the formation of PGs, thromboxanes, and leukotrienes by reducing the release of arachidonic acid and constitutes the most important mechanism of the anti-inflammatory effect of NSAIDs (Vane and Botting 1996).

Non Steroidal Anti-inflammatory Drugs

Classic NSAIDs are the most preferred drugs in the treatment of inflammatory diseases because they are effective in relieving pain, fever, redness and odema (Mitchell and Warner 1999, Ferreira 2002). The anti-inflammatory effects of these drugs are lower than those of SAEDs. However, the combination of the three effects mentioned above has increased the use of NSAIDs considerably. In addition, one of the most important reasons why NSAIDs are primarily used in inflammation, pain and fever today is that they are not addictive like narcotic analgesics (Amadio and Cummings 1993) and there is no tolerance to their effects (Kayaalp 1998). When we take a look at the short history of NSAIDs, it is noteworthy that colchicine was first described in 1820, salicylic acid was described in 1860, and the first Aspirin tablet was

synthesized in 1898 (Flower 1999). The first use of the name NSAID in 1949 coincided with the synthesis of phenylbutazone. In 1971, this adventure started with Dr. John Wyane's studies on the mechanisms of action and his identification of the first cyclooxygenase enzyme added a new dimension and paved the way for the Nobel Prize (Abramson and Weismann 1989). In 1976, prostaglandin endoperoxide synthetase cyclooxygenase (COX) enzyme, a new stop in the adventure, was obtained, thus studies on the mechanisms of action, side effects and safety profile of NSAIDs were accelerated. The latest development on this subject came in the early 1990s when it was shown that COX is not a single molecule but has multiple isomers, and each isomer plays a role in different functions. Thus, clinical studies have gained a new dimension (Simon 1999, Laudanno et al. 2001).

Mechanisms of Action of NSAIDs

The anti-inflammatory effect mechanisms of NSAIDs can be listed as inhibition of the synthesis of COX and lipoxygenase (LO) products, inhibition of toxic oxygen radicals and lysosomal enzyme release, prevention of neutrophil aggregation, adhesion and chemotaxis, and uncoupling of oxidative phosphorylation. The enzyme in the prostaglandin synthesis pathway is the COX enzyme (Fierro and Serhan 2001). This enzyme converts arachidonic acid into unstable PGG2 and PGH2. Today, it is known that there are two forms of cyclooxygenase called COX-1 and COX-2 (Rajni et al. 2003). COX-2 is induced at the inflammatory site by cytokines, inflammatory mediators, endotoxins and mitogenic agents (Mitchell and Belvisi 1994, Farraz et al. 1997, Michaluart et al. 1999,). The basic form, which we call COX- 1, is found in many normal cells and tissues such as platelets, vascular endothelium, gastric mucosa, kidney, pancreatic islets of Langerhans, seminal vesicles and brain (Mitchell and Warner 1999, Tegeder et al. 2000). However, COX-2 can be produced in some areas of the kidney and brain (Breder et al.1995, Harris et al.1994). While COX-1 is found in the stomach, COX-2 is not found in the stomach. This shows that selective COX-2 inhibitors have less side effects on the GIT. LO products are formed from arachidonic acid via the 5-lipoxygenase enzyme. NSAIDs prevent prostaglandin synthesis by inhibiting the cyclooxygenase pathway, but they cannot inhibit the lipoxygenase pathway and cannot prevent leukotriene formation. Aspirin inhibits both COX-1 and COX-2 enzymes by making covalent bonds. The primary effect of all other NSAIDs, which are reversible cyclooxygenase inhibitors, is related to the pharmacokinetic clearance of the drug. NSAIDs are roughly divided into two groups with half-lives shorter than 6 hours and longer than 10 hours. There is

substantial evidence that therapeutic doses of aspirin and other NSAIDs reduce prostaglandin biosynthesis in the human body (Livingston 2000, Simon 1999 , Cirino 1998). And a significant correlation has been observed between the anti-inflammatory activities of these drugs and their potential to inhibit cyclooxygenase (Dunne 1990, Vane and Botting 1996). However, there are some exceptions, but these exceptions are attributed to the use of experimental environments that cannot mimic the in vivo environment (Mitchell et al. 1993). Although many findings indicate that the primary therapeutic effect of NSAEDs occurs through prostaglandin synthesis inhibition, it has also been determined that NSAEDs suppress IL-1 secretion by helper T lymphocytes by stimulating suppressor T lymphocytes. Cytokines other than IL-1 are also released from macrophages and fibroblasts activated in inflammation. IL-6, TNF and interferon also play a role in inflammation. It has been shown in various studies that NSAIDs inhibit the production and release of IL-1 and IL-6 (Shinde et al. 1999). In inflammatory joint diseases, the number of polymorphous nucleated leukocytes increases in the synovial tissue and cartilage surfaces, and proteolytic enzymes, like other mediators, are released from them. These enzymes cause the onset of inflammation and also the destruction of periarticular bone. NSAIDs also show their effects by providing lysosomal membrane stabilization and preventing the release of lysosomal enzymes. It is also suggested that they inhibit the release of lysosomal enzymes by increasing the level of cAMP (Shinde et al. 1999). It has been shown in various studies that NSAIDs inhibit the formation of free oxygen radicals in inflamed tissue or bind and inactivate them (McCord and Roy 1982). Other properties of NSAIDs that contribute to their anti-inflammatory effects are; include preventing neutrophil aggregation, adhesion and chemotaxis, and antagonizing NADPH oxidase and phospholipase C activity (Abramson and Weismann 1989, Brooks and Day 1991).

Places Where NSAIDs Are Used

When these drugs are used as analgesics, they are generally effective against mild pain such as toothache (Amadio 1993). They do not have the undesirable effects of opiates on the central nervous system (respiratory dysfunction, increased physical dependence). NSAIDs lower body temperature in febrile states, but do not change normal body temperature. In fact, select COX-2 inhibitors have effective antipyretic effects. Treatments of rheumatoid arthritis and osteoarthritis are among the basic clinical applications of NSAIDs (Karaaslan 1993). The suppression of inflammation without gastric toxicity in chronic treatment of patients with rofecoxib and celecoxib shows that selective

COX-2 inhibitors are more advantageous than other NSAIDs. In general, NSAIDs only provide relief from the symptoms of inflammation and pain caused by the disease, they cannot prevent the progression of the pathological damage caused by the disease to the tissues. Other uses of NSAIDs depend on their ability to inhibit prostaglandin biogenesis. Prostaglandins also take part in the development of the ductus arteriosus. For this reason, indomethacin and similar agents are used to close unclosed ducts in newborns. On the other hand, the use of non-selective NSAIDs in pregnant women may cause premature contraction of the intrauterine ductus arteriosus. It has been determined that prostaglandins (vasodilator PG) synthesized by COX-1 and COX- 2 in fetal life are effective in maintaining the patency of the ductus arteriosus (Clyman et al. 1999). It is necessary to be cautious in the use of selective COX-2 inhibitors in pregnant women, as they prevent the formation of isoforms that keep the fetal duct open. Prostaglandins released by the endometrium during menstruation may be the cause of other symptoms and severe cramps in primary dysmenorrhea, which is treated with NSAIDs. A new study found that the selective COX-2 inhibitor refecoxib is as good as naproxen sodium in treating dysmenorrhea. It has been found that the major mediator of hypotension and severe vasodilation in patients with systemic mastocytosis is PGD2, which is released in large amounts from mast cells. Treatment of these patients with antihistamines alone is not effective, but these episodes can be effectively prevented by adding NSAIDs to the treatment (Roberts and Oates 1991). PGE2 has also been found to be associated with humoral hypercalcemia in some cancers. Treatment with NSAIDs effectively reduces serum calcium levels in some patients (Brenner et al. 1991). An important use of NSAIDs is the prevention of colon cancer. Epidemiological studies show that frequent aspirin use causes a significant and striking decrease in the incidence of colon cancer (Thun et al. 1991). Interestingly, this decrease is achieved with a dose as low as 4 or 6 325 mg tablets per week.

Side Effects of NSAIDs

The most common side effects associated with the use of NSAIDs are gastrointestinal system side effects. GI symptoms; dyspepsia (Bures et al.2002). It is distributed in a wide spectrum such as gastric erosion, peptic ulcer, upper GI bleeding (Bures et al. 2002), and intestinal inflammation (Wallace 1997, Rainsford 1999). GIT intolerance is reported to be 30%, and the prevalence of endoscopic ulcers is reported to be 10–30%. In Europe, 400 out of 1000 people hospitalized every day due to upper GI bleeding are directly attributed to NSAIDs. In the genitourinary system; Decrease in glomerular filtration, acute

renal failure, papillary necrosis, increase in serum creatinine level, water retention, and proteinuria may occur (Favre et al. 1982, Favre et al. 1983, Henry 1990, Ruiz and Lowenthal 1997, Wallace 1999, Basivireddy et al. 2004,). In the respiratory system; bronchospasm, asthma provocation (Henry 1990). and pneumonitis is not uncommon. In the liver; Various disorders such as toxic hepatitis (Purcell et al. 1991), cholestatic jaundice, liver failure (Bort et al. 1999), Reye Syndrome (Pinsky et al. 1988) may occur. Neuropsychiatric side effects are seen with the emergence of problems such as headache, dizziness, drowsiness, tinnitus, depression, confusion, and hallucination (Hasçelik 2002). It has been reported that cognitive dysfunction, memory loss, irritability, insomnia, concentration impairment, forgetfulness, personality changes and even paranoid reactions are also observed (Horatio et al. 1999). It is known that these side effects are more common in elderly patients and that these side effects occur more frequently when using high doses. Dermatological side effects: It may occur as urticaria (Matthieu et al. 2004), leukocytoclastic vasculitis, erythema multiforme (O'brien 1986, Ernest and Egge 2002), drug eruption, morbilliform eruptions, vesiculobullous eruptions, exfoliative erythrodermia, photosensitivity (Grundmann et al. 2001). Additionally, toxic effects such as Stevens Johnson Syndrome and toxic epidermal necrolysis are also mentioned. Hematological side effects are bleeding tendency (Schulman and Henriksson 1989), aplastic anemia (Clinch and Waller 1989), thrombocytopenia, and agranulocytosis (O'brien 1986). NSAIDs increase blood pressure in patients with hypertension due to their inhibition of prostaglandin synthesis (antinatriuretic effects and tendency to vasoconstriction) (Pope et al. 1993, Frishman 2002). It has been shown in various studies that NSAIDs, like salicylates, disrupt glycosaminoglycan synthesis and increase the loss of proteoglycan, the basic substance of the cartilage matrix. In joint diseases characterized by inflammation, they disrupt proteoglycan synthesis and increase the resorption of the extracellular matrix (Rainsford et al. 1999).

Contraindications of NSAIDs

NSAIDs should not be used in individuals with a history or symptoms of gastrointestinal bleeding. It should not be used in pregnant women as it prolongs the duration of pregnancy and increases the tendency for low-birth-weight babies and pre- and post-natal bleeding (Kayaalp 1998). The use of NSAIDs, especially aspirin, especially in children with viral infections, should not be used in childhood viral infections, as they cause Reye Syndrome, which can be fatal (Pinsky et al. 1988). On the other hand, NSAIDs are contraindicated in people with a history of asthma because they provoke asthma (Henry et al. 1990).

3.REFERENCES

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Chapter 5

Robotic Surgery Training and the Role of Nurse in the Robotic Surgery Process

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ABSTRACT

With the rapid development of robotic surgery, which is managed with the help of a control unit, which allows the physician to remotely control surgical instruments and perform applications through computer-based robots, and which allows surgical interventions to be performed more easily, there has been a rapid increase in their use. Accordingly, the necessity of establishing robotic surgery teams and training these teams has come to the fore. In the training of nurses working in the field of robotic surgery; It is suggested that the introduction of robotic systems, cleaning and sterilization of instruments, installation of equipment, patient preparation, position and position of robotic arms, connecting the image unit, emergency procedures and defining the roles and responsibilities of nurses should be included. Considering that the use of robots with different features in the surgical field will increase today and in the future, it is seen that it is important to examine the increasing roles and responsibilities of the nurses in this team. In this review, it is aimed to examine the robotic surgery training and the roles of nurses working in the field of robotic surgery. It is thought that the study will contribute to the nurses working in the units that use or will use robotic surgery technologies.

Keywords: *Nursing, Robotic surgical procedures, Surgery.*

INTRODUCTION

Robotic surgery is surgical interventions which are performed by using computer-based robots, which are managed with the help of a control unit that allows physicians to remotely control surgical instruments and which allow for easier implementation of complex surgical interventions (Oztepe Yesilyurt and Ozsoy Durmaz, 2023; Yavuz Karamanoglu and Demir Korkmaz, 2013; Karaismailoglu and Cilingir, 2020; Uslu et al., 2019).

The first robotic surgery attempt in the world was performed in 1985 for biopsy in neurosurgery (Celik, 2011; Kılınç Akman et al., 2022). Over the years, with the rapid development and spread of da Vinci robotic surgery systems around the world, the use of robotic surgery has become widespread and popular in general surgery, orthopaedic surgery, thoracic surgery, urological surgery, cardiovascular surgery, gynaecological surgery, plastic surgery and otolaryngology surgery (Oztepe Yesilyurt and Ozsoy Durmaz, 2023; Karaismailoglu and Cilingir, 2020; Kılınc Akman et al., 2022; Raposa et al., 2020; He et al., 2021).

Although robotic surgery systems cannot be accessed in every country around the world, a rapid increase in their use can be seen (Kılınc Akman et al., 2022; Kang et al., 2016). In countries where robotic surgery is applied, this system is known to make surgery easier and improved surgery outcomes are reached through these systems (Kang et al., 2016; Okgun Alcan et al., 2019).

The reason why robotic surgery has progressed so rapidly and is accepted in almost every field of surgery is attributed to advantages of these interventions (Oztepe Yesilyurt and Ozsoy Durmaz, 2023; Yavuz Karamanoglu and Demir Korkmaz, 2013). Robotic surgery practices are known to provide minimal scarring and improvement in cosmetic appearance with smaller surgical incision, reduce hospital stay and costs of nursing care by decreasing the risk of pain, infection and hemorrhage, facilitate access to organs, tissue and nerves by allowing three-dimensional imaging and provide surgeons with ergonomic position (Okgun Alcan et al., 2019; Porto ve Catal, 2021; Cepolina and Razzoli, 2022; Martins et al., 2019; Porto, 2020). In addition to the advantages of robotic surgical interventions, factors such as the high cost for purchasing, installing, maintaining robotic surgical systems, tools' being large, long installation time, difficulty in changing camera and port locations, physicians' working without a sense of touch and lack of experience and lack of information in health professionals constitute the disadvantages of these interventions (Celik, 2011; Porto, 2020; Abboudi et al., 2012; Akgul and Yildiz, 2011).

When all these advantages/disadvantages in the field of robotic surgery are considered, it is stated that the best surgical results can be achieved with robotic

surgery team and there should be perioperative nurses, surgeons, surgical assistants and anesthetists in this team (Oztepe Yesilyurt and Ozsoy Durmaz, 2023; Giedelman et al., 2021; Brusco, 2012). For more effective use of robotic surgery and better results, the whole team should be informed on the subject and they should participate in training programs about robotic systems (Karaismailoglu and Cilingir, 2020; Kang et al., 2016; Brusco, 2012; Francis, 2006). It is seen that it is important especially for nurses to receive education in this field (Oztepe Yesilyurt and Ozsoy Durmaz, 2023; Porto and Catal, 2021).

Considering that the use of robots with different features in the surgical field will increase today and in the future, it is seen that it is important to examine the increasing roles and responsibilities of the nurses in this team (Oztepe Yesilyurt and Ozsoy Durmaz, 2023; Porto and Catal, 2021).

In this direction, the aim of this review is to examine the robotic surgery training program and the roles of nurses working in the field of robotic surgery.

Nursing Training Program in Robotic Surgery

Professional roles of nurses for robotic surgery systems that emerge with technological methods and improve continuously are increasing by expanding. Therefore, the necessity for nurses to receive special training in order to improve themselves and to gain experience about robotic surgery has come to the fore (Uslu et al., 2019; Kang et al., 2016). The trainings that should be given in this field of surgery where complex instruments are present include;

- Introducing robotic systems,
- Cleaning and sterilization of robotic instruments,
- Installation of equipment,
- Patient preparation and positioning, placing the robotic arms,
- Connecting the display unit,
- Roles and responsibilities of nurses,
- Emergency procedures (Karaismailoglu and Cilingir, 2020; Francis, 2006; Zender and Thell, 2010).

Introduction and Installation of Robotic Systems

Introduction of robotic systems should include information about hardware and terminology about robotic surgery and installation of the system (Yavuz Karamanoglu and Demir Korkmaz, 2013; Uslu et al., 2019). It is extremely important to learn about robotic hardware and system parts, and to master the maneuvers of robotic arms (Francis, 200). Robotic surgery nurse should know the manoeuvres of robotic arms, how to connect and separate the parts of the system, and how to equip the robotic arms and the camera. In order to place the

robot in the operating room and to protect the hardware systems from damage, robotic surgery nurses should get help from authorized persons during the installation of the system by labeling the connection points of the monitor and recording devices and making the black/white color settings of the cameras (Yavuz Karamanoglu and Demir Korkmaz, 2013). The surgeon's console should be positioned on the same side as the surgeon on the operating table to ease communication (Akgul and Yildiz, 2011). Nurses are also responsible for preparing the robotic instruments, delivering these to the surgeon in a controlled and safe way, being careful about sharp objects and sterilizing the instruments (Yavuz Karamanoglu and Demir Korkmaz, 2013).

Cleaning and Sterilizing the Robotic Instruments

Robotic surgical instruments require special care as they are different from laparoscopic instruments. The circulating nurses are not responsible for the cleaning of these instruments. However, they should know the mechanics of the instruments, their details, decontamination and sterilization processes. Robotic surgery nurses should collect the necessary information about the instruments that surgeons frequently use for different procedures, and they should arrange the trays in the operating room. Collecting and evaluating information from all users of the system and making material and instrument changes are the responsibilities of robotic surgery nurses. In addition, nurses should record the number of uses of the instruments in robotic surgery applications (Yavuz Karamanoglu and Demir Korkmaz, 2013).

Surgeon's console, patient unit, display unit and system cables should be wiped with a soft, non-marking cloth moistened with antibacterial soapy water and dried well. Touch screens should be cleaned with detergent and water (Pamir Aksoy et al., 2011).

Robotic surgical instruments should be sterilized respectively (Yavuz Karamanoglu and Demir Korkmaz, 2013). Robotic surgical instruments have a limited usage time (Brenk, 2009). Therefore, these instruments should be washed in the sterile area at the end of the procedure. This way, bodily fluids are prevented from drying in/on the instrument, they are cleaned, taken into buckets of dirty instruments and delivered to the washing section of the central sterilization unit after counting. Ultrasonic washing machine should be used for cleaning the ports used for aspirator purposes (Yavuz Karamanoglu and Demir Korkmaz, 2013). In the delivery process, the instruments are counted; in the sterilization process, the instruments are checked for damage, and the packages are checked for tears and torn. In the preparation of Endowrist instruments used in Intuitive Surgical and electro surgery, greasers to prevent tissue adhesion

should be used (Yavuz Karamanoglu and Demir Korkmaz, 2013; Pamir Aksoy et al., 2011).

Positioning the Patient and Placing the Robotic Arms

Patient positioning and port placement play an important role in the ergonomy of surgical intervention to be carried out. Appropriate positioning of the patient not only ensures that every member of the surgical team (patient assistant, surgical nurse, anaesthetist) have equal access to the patient but also ensures an optimal placement between the target organ and the robot. With simulations performed in operating rooms, it is possible to learn how to place the ports correctly to the mannequins and to access to patients, and also the procedures to disconnect the patient from the robot in an emergency (Shidhar et al., 2017). Patient position in robotic surgery interventions are similar to positions in laparoscopic surgery, while it includes some differences. It is known that some surgeons prefer to rotate the operating table to ensure the proper clamping of the robotic arms to the patient. During the positioning of the operating room table and the patient, the circulating nurse is responsible for placing the robotic arms and arranging the room in accordance with the light (Yavuz Karamanoglu and Demir Korkmaz, 2013). Since the robotic arms, which are one of the robotic components, are very large, it is of great importance to position the arms correctly in order to prevent arms from colliding with each other, camera assistants or the patient. It is very important to correctly position the robotic arms the first time since it is not possible to reposition the patient after robotic arms are placed (Ersayli and Bayindir, 2011).

Robotic arms should be placed to prevent the contamination of sterile clothes. In particular, robotic arms should be placed in such a way they donor prevent the contamination of operating room lights, video panel and intravenous lines (Francis, 2008).

In addition, in order to prevent complications that may develop in robotic surgery due to patient positioning, it is important to take safety precautions again in long-lasting operations and to take a break when necessary (Kilinc Akman et al., 2022; Song et al., 2013).

Connecting the Display Unit

Display unit; It is a three-dimensional system consisting of a large monitor with a high resolution image and touch feature, and shelves with auxiliary surgical equipment. During the operation, it ensures that the team can follow the procedures and make necessary interventions by observing possible changes. In addition, this unit provides carbon dioxide insufflation and video recording is

also possible (Yavuz Karamanoglu and Demir Korkmaz, 2013; Karaismailoglu and Cilingir, 2020).

Robotic surgery nurse also has duties such as installing the parts of the instrument, making the connections, preparing the instrument, providing the white and black balance of the camera and laparoscopes and covering the patient (Yavuz Karamanoglu and Demir Korkmaz, 2013). It is known that during robotic surgery procedure, nurses show and interpret the messages on robotic screen monitor, allowing the surgeon to concentrate on the surgical procedure and therefore play a role on the course and success of the surgery (Yavuz Karamanoglu and Demir Korkmaz, 2013; Ucuzal and Kanan, 2008).

Roles and Responsibilities of Nurses

Nursing practices always adapt to the development of new technologies. However, these adaptation processes may also cause dissatisfaction in nurses and problems in work flow (Frith, 2021). In this case, since robotic surgery is a specialized field, definition of the increasing roles and responsibilities of nurses has come to the fore (Yavuz Karamanoglu and Demir Korkmaz, 2013; Karaismailoglu and Cilingir, 2020). The roles and responsibilities of nurses in robotic surgery are defined as;

Nursing Roles in Preoperative Period;

- Taking anamnesis from the patient; to have extensive information about the individual characteristics, past problems, current diseases and health history of the patient's family, to determine the possible risks according to the surgery that the patient will undergo and to take the necessary precautions (Dincer and Alemdar, 2018),
- Preparation of the patient (changing clothes, trimming the hair of the operation area, ensuring that the stomach is empty, etc.) (Celik, 2011; Dincer and Alemdar, 2018),
- Explaining to patients who are worried before surgery that a robot will operate on them that robotic surgery systems work with the guidance of the surgeon connected to a computer and that they do not work automatically (Celik, 2011),
- Preparation and control of the system, control of the expiration dates of the materials, placement of the patient, positioning the patient, ensuring the safety of the team (Yavuz Karamanoglu and Demir Korkmaz, 2013; Celik, 2011; Dincer and Alemdar, 2018),

- Checking whether the operating room is clean and making sure that there are no medical records of the previous patient in the room (Pamir Aksoy et al., 2011),
- Checking and controlling the instruments before surgery, setting the instruments, making the required checks throughout the surgery, placing and positioning the patient (Yavuz Karamanoglu and Demir Korkmaz, 2013; Kilinc Akman et al., 2022; Raposa et al., 2020; Ben-Or et al., 2013),
- Training patients and staff (Yavuz Karamanoglu and Demir Korkmaz, 2013),
- Making sure that the products to be used in robotic surgical interventions are usable, reliable and applicable, deciding on whether the products are effective, their costs, and which products can be used socially, legally and ethically (Cetin, 2018),

Nursing Roles in Intraoperative Period;

- Nurses should know the system well, plan to position the patient in the limited space in the best way, and help the surgeon to end the surgery in a healthy and fast manner (Dincer and Alemdar, 2018),
- Must know the sterile and non-sterile parts of the robot by following the aseptic principles and pay attention to the following up the sterile parts (Dincer and Alemdar, 2018),
- The scrub nurse should place the sterile table right next to the patient and order the instruments according to the surgical intervention (Dincer and Alemdar, 2018),
- Ensuring patient safety, checking whether the support pads used in positioning patients are properly positioned (Kilinc Akman et al., 2022),
- Ensuring the safety of the team and the patient, helping the surgeon, following the sterile and non-sterile areas by paying attention to asepsis rules (Yavuz Karamanoglu and Demir Korkmaz, 2013; Raposa et al., 2020),
- Preserving the sterility of gowns in long-lasting interventions, monitoring for mottling on the pressure points of the patients' arm and legs in terms of rhabdomyolysis (Kilinc Akman et al., 2022),
- Supporting the elbows with soft pads to prevent ulnar nerve injury caused by the patients' arm being bent especially in the supine position (Kilinc Akman et al., 2022),

- Preventing and monitoring the pressure caused by belts/splints, etc. used in leg fixation to prevent lower extremity nerve damage (Kilinc Akman et al., 2022),
- Preventing the development of corneal abrasions by covering the patients' eyes with soft pads during the surgery (Kilinc Akman et al., 2022; Frith, 2021),
- Monitoring pressure of cuffs attached to the extremities according to position changes, monitoring compartment syndrome that may develop due to excessive pressure-related fluid collection (Kilinc Akman et al., 2022),
- Monitoring of excessive blood loss and hypotension that may develop due to being in trendelenburg position for a long time (Kilinc Akman et al., 2022),
- Placing the robot on the patient's body, reading and interpreting the messages on the monitor (Yavuz Karamanoglu and Demir Korkmaz, 2013; Raposa et al., 2020),
- With the break in interventions lasting for more than three hours, discussing whether pneumatic compression is necessary for the patient and whether nurse change is required, repeating the surgical counts (Kilinc Akman et al., 2022),
- Implementation of the necessary interventions and keeping surgical operation sets ready to manage power deficiencies that may develop and to switch to laparoscopic or open surgery when necessary (Uslu et al., 2019; Okgun Alcan et al., 2019; Giedelman et al., 2021; Ben-Or et al., 2013),
- Managing the operation lists, helping with all procedures and research interventions during surgery (Yavuz Karamanoglu and Demir Korkmaz, 2013),
- Should prepare detailed documentation lists of the materials used for patient safety, count the materials in line with this list after the surgery is over, record them, and not allow the patient to leave the operating room before the number is verified (Celik, 2011; Dincer and Alemdar, 2018).

Nursing Roles in Postoperative Period;

- Patient care after robotic surgery is similar to the care of patients undergoing open surgery. In the post-operative care process of nurses; It has duties and responsibilities such as ensuring airway patency, monitoring vital signs, following up bleeding and wound care, auscultation to bowel sounds, informing the patient and his family,

monitoring the patient for signs and symptoms of infection (Dincer and Alemdar, 2018).

- In addition, have responsibilities to plan and implement patient's early discharge training (Celik, 2011; Dincer and Alemdar, 2018).

Emergency Procedures

When an emergency develops during the robotic surgery procedure, the team members are instructed to secure the robot safely and to disconnect the robot quickly from the surgery area (Zender and Thell, 2010). Meanwhile, robotic surgery nurses are required to disconnect the robotic system from the patient and start the emergency procedure (Yavuz Karamanoglu and Demir Korkmaz, 2013).

For the possibility of switching from robotic surgery to open surgery procedure, the team should always have the ability to create the suitable environment for emergency open surgery and have all the necessary instrument ready in the operating room (Brenk, 2009). In addition, robotic surgery nurses should know about all the emergency procedures to turn on the robot manually, when necessary (Yavuz Karamanoglu and Demir Korkmaz, 2013).

RESULTS AND DISCUSSION

With the implementation of robotic surgery in more difficult and more complicated surgical interventions, more responsibilities have been placed on the members of the robotic surgery team. It has been found that it is necessary for nurses to participate in robotic surgery programs to ensure their adaptation to this field with the addition of new roles/responsibilities of nurses.

Robotic surgery trainings and practices make surgery easier for nurses and also help nurses to have experience in terms of implementing developing technologies and developing their professional roles.

In this context, it is thought that the present study will be a guiding resource in planning future studies on nursing education programs in the field of robotic surgery and will guide the literature.

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Chapter 6

Quantifying The Maximum Skin Defect Size Allowing Primary Closure in Each Aesthetic Subunit Following Benign Facial Tumor Excision

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Summary

This chapter delves into the maximal permissible dimensions of cutaneous defects that can be sustained in various aesthetic subunits of the face after benign tumor excision, with the aim of facilitating primary closure without incurring aesthetic or functional compromises.

The primary objective is to provide a guideline for healthcare practitioners on the limitations of tumor dimensions in different facial subunits, in order to achieve successful primary closure post-excision.

A retrospective review of medical and photographic records from 2013-2021 was carried out. Patients were categorized based on the type of tumor excision (benign skin tumor, cheek tumor, nevus) and further stratified by the sublocation on the face. Lesion dimensions were measured using AutoCAD® 2019 software, with an emphasis on identifying the largest tumor dimensions that allow for complication-free primary closure.

The chapter presents an analysis of cases distributed across various facial subunits: Periorbital (185), Perioral (274), Forehead (280), Cheek (348), Nasal (157), and Auricular (41). Guidelines for maximal permissible tumor dimensions for primary closure in each facial subunit are established.

Although benign skin tumor excisions in facial subunits are generally successful, to minimize complications and yield more predictable results, further research with larger patient cohorts is recommended.

Keywords: Aesthetic; Cutaneous Defects; Dermis; Face; Skin Neoplasms

INTRODUCTION

Clinically benign skin lesions are typically diagnosed and monitored through routine examinations.(Blum, Zalaudek, & Argenziano, 2008) However, in instances where a lesion raises suspicion during examination, it is excised and then subject to histopathological analysis.(Chathra & Bhat, 2016) Excision of skin lesions from the face is one of the main workload of dermatosurgery. One of the significant hurdles is deciding the optimal strategy for closing the skin after tumor excision. A major challenge lies in deciding the optimal strategy for closing the skin after tumor excision.

The method to manage the skin defect hinges on two key factors: the wound's size and its proximity to facial sphincters.(Xie et al., 2021) Areas like the eyebrow and nasal rim, due to their unique anatomy, require special consideration to ensure the aesthetic outcome is optimal.(Shah, Zoumalan, & Constantinides, 2008) In some cases, to circumvent functional or aesthetic complications, it may be necessary to employ advanced surgical strategies, including local flaps and skin grafts.

The type of surgery chosen directly influences the extent of preoperative preparations. It also determines whether the patient will need hospitalization or if the procedure can be conducted on an outpatient basis.(McGillis & Stanton-Hicks, 1998)

In this paper, we aim to share our insights to pinpoint the largest size of a skin defect in each facial subzone that can undergo primary closure, without compromising aesthetic or functional outcomes.

METHODS

We retrospectively examined the medical and photographic archives from the Plastic, Reconstructive and Aesthetic Surgery Clinic at Local University (LPRAS) for the period spanning 2013 to 2021. We consolidated data from procedures coded as benign skin tumor excision, cheek tumor excision, and nevus removal. The study population included patients aged between 18 and 50 years.

Epicrisis-related facial area excisions were singled out. We categorized patients diagnosed with dermal nevus, seborrheic keratosis, xanthoma, solar lentigo, sebaceous hyperplasia, nevus sebaceus, dermatofibroma, hemangioma, pyogenic granuloma, and cornu cutaneum. These patients' images were then sourced from the LPRAS photo archives. In the end, preoperative photos from 1285 patients were found suitable for this study.

Patients were classified according to the location of the facial subzone excisions: periorbital, perioral, forehead, nasal, auricular, and cheek areas. These

zones were further subdivided into subzones, following the standard classification in Plastic Surgery literature.

Photographs were taken with Canon EF 100mm f/2.8L Macro lens with Canon EOS 600D. Images were analyzed using the 2019 version of AutoCAD® software to assess lesion dimensions. The corneal diameter (white-to-white) was used as the reference length during photo-based measurements. We evaluated lesion width perpendicular to the Langer's lines and documented the largest tumor dimension that permitted primary closure without complications for each subzone. We also compiled data on the most common complications following excisions in the respective subzones.

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was initiated with the approval of Clinical Research of Local University Faculty Clinical Research Ethics Committee 2011-KAEK-27/2021-E.2000188390 no.

RESULTS

The distribution of patients according to the facial subzones where lesions were found is as follows: periorbital (185 patients), perioral (274 patients), forehead (280 patients), cheek (348 patients), nasal (157 patients), and auricular (41 patients). The cheek area was most commonly subjected to primary repair after excision.

With respect to Fitzpatrick skin type distribution, roughly half of the patients were characterized as type 3, while a combined total of 724 patients were identified as types 2 and 4. A comprehensive breakdown of the subzones is provided in Table 1.

Periorbital region: Dermal nevus and xanthelasma were the most commonly diagnosed pathologies within this area. The upper eyelid subzone was not frequently chosen for tumor excisions; however, 6 instances of cutaneous horn and 6 of skin tags were observed and removed. The maximum defect size conducive to primary closure in the upper eyelid subzone was determined to be 15 mm. The most common complication observed in this area was temporary lagophthalmos. The lower eyelid subzone, on the other hand, was a frequent site for dermal nevi. The maximum defect size for primary closure in this subzone was noted to be 4 mm, with transient scleral show as the leading complication. The medial canthal subunit was most commonly associated with xanthelasma, with transient epiphora being the primary complication encountered.

Interestingly, no complications were reported within the lateral canthal subunit. (Figure 1)

Fig 1: Transient Epiphora after excision from medial canthal area

Perioral region: The melolabial subunit, a natural crease situated between the cheek and orbicularis oris, demonstrated a maximum defect dimension of 22 mm for successful primary closure. The labiomental subunit, another natural crease, saw successful primary closure following the excision of 25 lesions. The philtrum, a unique and relatively small subunit, had 18 lesion excisions with a maximum defect dimension of 3 mm allowing for primary closure. The predominant pathological diagnosis for the perioral region was dermal nevus. Wound dehiscence was the primary complication in all subunits with the exception of the philtrum(Figure 2). Notably, in the philtral subunit, distortion of the philtral columns emerged as a common complication following excisions.

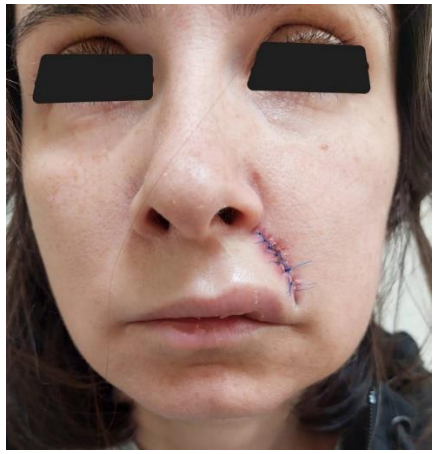

Fig 2: Transient distortion of upper lip

Forehead region: The central forehead subunit, a conspicuous region on the face, presented a diversity of pathological diagnoses. Of the 47 excised lesions, the primary diagnoses were dermal nevi, sebaceous hyperplasia, and nevus sebaceus. The temple and supraciliary-eyebrow subunits frequently exhibited seborrheic keratosis and dermal nevi. The forehead region presented the most significant variability in maximum defect dimensions amenable to primary repair, attributable to the varying thickness and elasticity of forehead skin. The most prevalent complication for the glabellar subunit was the approximation of eyebrows, while dehiscence was the primary complication for other subunits.

Cheek region: The cheek, rich in fibrofatty tissues, displayed considerable resilience in accommodating skin defects. Specifically, the infraorbital subunit could sustain a skin defect up to 30mm that still allowed for primary repair. Close to 200 lesions were excised from the mandibular and zygomatic subunits, with dehiscence being the most common complication encountered.

Nasal region: The skin texture of nasal subunits is notably distinct from the rest of the facial skin. The fibrofatty tissue is more prevalent in the tip, ala, and soft trigon subunits. The skin of the columella serves as a transition zone between the upper lip and the nasal tip. Post-surgical complications from excisions in the nasal dorsum commonly included transient tip elevation. The nasal ala and nasal tip subunits frequently exhibited sebaceous hyperplasia, with dermal nevi also being a common diagnosis in this region. Notable complications following defect closure in the nasal alar subunit included distortion, as well as internal and external nasal valve failure (Figure 3). Owing to their small size, the excision of lesions greater than 1mm in the soft trigon subunit and columella often resulted in distortion (Fig 4).

Fig 3: Excision of small lesions from alar crease can cause internal valve deficiency

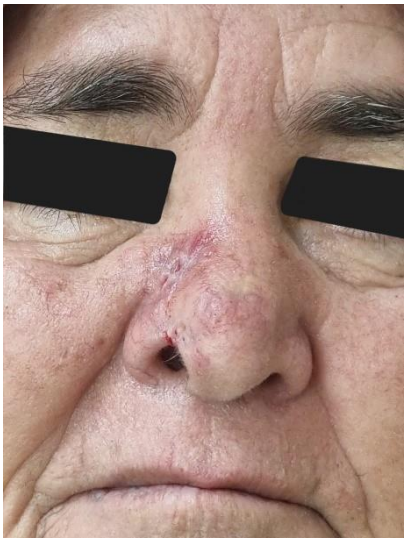

Fig 4: Excision from alar crease caused distortion of alar rim.

Auricular region: The conchal subunit most displayed diagnoses of seborrheic keratosis. The posterior auricular subunit was associated with a variety of pathological diagnoses, including dermal nevi and nevus sebaceus. The helix, as the most prominent subunit of the auricular region, frequently exhibited diagnoses of solar lentigo and dermal nevi. Excisions conducted in the auricular region were generally successful, with dehiscence being the most prevalent complication.

Table 1: Maximum dimensions that allowed primary repair for facial subunits and most frequent pathologic diagnosis.

Facial Zones/Subzones	Number of Patients	Most Frequent Diagnose	Margin
Periorbital Area			
Superior Lid	15	Skin Tag	15 mm
Inferior Lid	54	Dermal Nevus	4 mm
Medial Canthus	86	Xanthalesma	6 mm
Lateral Canthus	30	Dermal Nevus	11 mm
Perioral Area			
Melolabial Crease	84	Dermal Nevus	22 mm
Labiomental Crease	25	Dermal Nevus	15 mm
Mentum	64	Dermal Nevus	20 mm
Filtrum	18	Dermal Nevus	3 mm
Upper Lip	61	Dermal Nevus	8 mm
Lower Lip	22	Dermal Nevus	8 mm
Forehead Area			
Glabella	105	Dermal Nevus	10 mm
Santral Forehead	47	Dermal Nevus	18 mm
Temple	57	S. Keratosis	16 mm
Suprasillier	41	Dermal Nevus	15 mm
Eyebrow	30	Dermal Nevus	10 mm
Cheek Area			
Infraorbital	146	Dermal Nevus	30 mm
Mandibular	112	Dermal Nevus	22 mm
Zygomatic	90	Dermal Nevus	23 mm
Nasal Area			
Tip	39	Dermal Nevus	5 mm
Ala	24	Dermal Nevus	2 mm
Soft Trigon	11	Dermal Nevus	1 mm
Dorsum	24	Dermal Nevus	23 mm
Lateral Wall	59	Dermal Nevus	23 mm
Auricular Area			
Concha	14	S. Keratosis	2 mm
Posterior Auricular	6	Dermal Nevus	7 mm
Tragus	6	Dermal Nevus	1 mm
Lobule	2	Dermal Nevus	1 mm
Helix	11	Solar Lentigo	2 mm
Helikal Root	*2*	Dermal Nevus	1 mm

DISCUSSION

Ensuring patient safety during surgical interventions is contingent on multiple factors. One paramount consideration is the selection of an appropriate anesthesia method. In outpatient procedures, local anesthetics are commonly employed. It's crucial for surgeons to be aware of the maximum safe doses of these anesthetics to avoid the risk of systemic toxic effects associated with high dosage.(Long et al., 2022) Based on our experience, the necessity for local anesthetics may significantly increase - by a factor of two with simple undermining of wound margins, and potentially triple or quadruple in the presence of additional flap or graft procedures. While simple excision and primary repair are typically performed as outpatient procedures, unforeseen circumstances can compromise the comfort and confidence of both the surgeon and the patient.

An inadvertent prolongation of a routine excision procedure can potentially precipitate significant ecchymosis. (Aydogdu et al., 2005) When ecchymosis manifests in facial regions, it invariably results in an aesthetically displeasing appearance, posing a considerable concern for patients with an active social life. Such a circumstance may necessitate the deferral of scheduled activities, thereby negatively impacting the patients' lifestyle and potentially reflecting unfavorably on the professional image of the surgeon. This underscores the need to carefully plan and execute these surgical procedures, taking into consideration the potential social and professional implications.

Prior to surgery, informed consent is secured from patients, during which they are apprised of the scope of the planned operation and the potential for resultant scar tissue. An unanticipated inability to achieve primary wound closure, necessitating supplementary surgical procedures, can engender legal repercussions. This underscores the importance of international stipulations such as the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, otherwise known as the Biomedical Convention. Article 5 of the Convention mandates that individuals be provided with comprehensive information regarding the purpose, nature, potential consequences, and associated risks of the surgical intervention. (8. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo) Adherence to this ethical requirement in medical practice is crucial, highlighting the importance of accurate preoperative planning and transparent communication.

During the excision of benign lesions, it is crucial to remember that skin is being diminished. While the skin over the oral and orbital sphincters can expand due to potent underlying contractions(Spicer, 1982), excisions from areas such as

the nasal tip, alar, and supra alar crease can lead to permanent deformities.(Barton, 1981) These deformities, even subtle, can reduce the cross-sectional area of the internal nasal valve, potentially resulting in persistent internal nasal valve failure.(Cole, 2003) Therefore, careful attention must be paid during excisions from the sebaceous skin that covers the caudal part of the nose, and patients should be thoroughly informed about possible functional failures.

The dermis, as the skin's key structural component, plays a crucial role in the resistance encountered during primary wound closure, creating consequential tension across the wound edges. In the cohort for this study, despite the absence of patients with Fitzpatrick skin type 5 and 6, patient inclusion was solely age restricted. This approach was predicated on the evidence indicating that while skin color and racial differences may not significantly affect dermal thickness or skin elasticity, age does indeed alter these parameters. (Inforzato et al., 2018; Takema et al., 1994; Whitmore & Sago, 2000) Using Fitzpatrick skin type classification as an absolute indicator of dermal variations across different racial groups may lead to inaccuracies in clinical judgement. (He et al., 2014)

In order to measure the size of the excised lesions from old photographs, it was necessary to refer to a distance of well-known length in the facial region, which did not differ much between people. When the white-to-white horizontal corneal diameter measurements made by different teams were examined, it was understood that this distance was 12 mm on average, with an average standard deviation of 0.3 mm.(Cruz et al., 2021; Venkataraman, Mardi, & Pillai, 2010) This value was taken as a reference in our study.

While calculating the distance based on the reference measurement, AutoCAD was used. Despite the availability of sophisticated algorithms specifically designed for preoperative planning and distance measurement, we opted for the simplicity and reliability of AutoCAD® for our calculations. The choice was influenced by its longstanding record of professional use and broad accessibility, setting it apart from many other software applications on the market.(Bodnar, Neimkin, & Holds, 2016) Although AutoCAD® is a simple software for the task, it has been demonstrated in the literature to successfully measure small distances on the face with a high degree of accuracy.(Parmar et al., 2020)

Complications encountered after excision of benign tumors from the face are often temporary or easy to deal with. However, care should be taken when excising lesions on the alar wing and alar crease. One of the components of the internal nasal valve is the fibrofatty tissue that forms the lateral nasal wall.(Cole, 2003) Care should be taken during excisions to be made from this area, and the

patient should be informed that he or she may have breathing problems for excisions over 2 mm.

Study Limitations: Despite the valuable insights presented in this study, several limitations should be noted. The retrospective design potentially introduces recall bias, affecting the accuracy of excision dimensions and post-operative outcomes. The use of AutoCAD® software on photographs, while precise, may not be as accurate as direct measurements. Finally, this study exclusively focused on the size of skin defects permitting primary closure without incorporating the influence of skin types, underlying health conditions, or lifestyle factors on wound healing and scarring. Future research should consider these factors for a more comprehensive understanding of primary closure outcomes in facial region.

CONCLUSION

The surgical intervention of benign tumors within the facial area, typically undertaken to enhance aesthetic appeal, characteristically results in outcomes that meet or exceed patient expectations. These favorable results, however, do not negate the need for rigorous scientific investigation. To truly minimize the risk of complications and establish a higher degree of predictability in patient outcomes, it is crucial that we extend our research to include a more extensive patient population.

Such concerted efforts will broaden our understanding of the varying nuances and intricacies involved in facial tumor excision. The resulting insights can then be utilized to refine surgical protocols, thereby ensuring optimized patient outcomes. Furthermore, these findings can contribute to a more informed patient-surgeon dialogue, fostering an environment where surgical expectations are accurately matched with probable outcomes.

In essence, the pursuit of excellence in this particular field of medicine requires a blend of practical expertise and continued scholarly research. The synergetic interaction of these two elements will not only enhance the quality of surgical outcomes but will also invariably contribute to the overall wellbeing and satisfaction of our patients.

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Chapter 7

Is There A Link Between Childrens'gastroesophageal Reflux Disease And Mothers' Psychopathology? A Case-Control Study

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ABSTRACT

Objective: Little but remarkable emphases have been laid on the relationship between Gastroesophageal Reflux Disease (GERD) and mother psychopathology. The studies have focused especially on the infancy period. In this study, the mothers of children belonging to a different age group (3-7 ages) were chosen, and obsessive-compulsive symptoms were reviewed for a change as well as depression and anxiety.

Methods: The case group is composed of mothers of 50 children diagnosed with GERD and the control group is mothers of 49 healthy children. The groups were matched according to age and educational status. The scales used in the study are Hospital Anxiety and Depression Scale and Maudsley Obsessive-Compulsive Inventory. Using chi-square, independent t-test and univariate analyses, both groups are compared with each other to find out whether there was a link between children's GERD and mothers' psychopathology.

Results: Anxiety and depression scores of the mothers in the study group are significantly higher than those of the control group. There are also significant differences between the two groups in terms of some feeding patterns such as food refusal, forced feeding and mother's regarding the child's feeding as insufficient. However, no significant difference was found in the obsessive-compulsive symptoms.

Discussion: These results should be assessed as important, external factors that affect the clinical process of a chronic disorder rather than being considered as a cause and effect relation. A distinctive increase in the risk of anxiety disorder and depression incidence in mothers in case of a chronic disorder like GERD needs to be considered important with regards to affecting both GERD's course and the mother-child relationship in a negative way.

Keywords: maternal psychopathology, feeding patterns, gastroesophageal reflux disease, psychiatry, child health

INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is the most common disease of the esophagus as well as one of the most frequent diseases among childhood diseases (Ambartsumyan & Rodriguez, 2014). Despite the fact that its mechanism is yet to be understood completely, it has been shown that it is related to genetic, environmental (cigarette, diet, etc.), anatomic, hormonal and neurogenic events(Vandenplas & Hassall, 2002) . In recent years, it has drawn attention as a risk factor in most upper respiratory diseases. It is known that GERD is related to otitis media, sinusitis, lymphoid hyperplasia, snoring, laryngeal edema and nodules (Rosbe et al., 2003). It is not possible to make a precise discrimination between pathological and physiological reflux since there is no gold standard diagnostic method and the data of incidence and prevalence are insufficient. It is predicted that the GERD prevalence among children is 1-8% in some publications, 2-7% in others(Karacetin et al., 2011) . In some conditions such as tracheoesophageal fistula, neurological disorder, oral motor dysphagia, its incidence may rise up to 70% (Hrabovsky & Mullett, 1985). The clinical findings of GERD may vary according to age in childhood. Findings obtained from the digestive system are generally observed postprandially (Davidson & Omari, 2000; Jung, 2001; Vandenplas et al., 2005). The main symptom among younger children is regurgitation and vomiting (Rerksuppaphol & Barnes, 2002). High frequency of vomiting and regurgitation may cause decreasing calorie intake, weight loss and growth retardation. Refusal to eat as well as vomiting is effective in weight loss. One of GERD's symptoms is a feeling of nausea among children old enough to express their complaints. Discomfort, crying and refusal to eat, dysphagia, and odynophagia may be observed among patients developing esophagitis-related acidic reflux. No relationship has been proven between the pain level and endoscopy and the degree of histological esophagitis (Harding & Sontag, 2000; Vandenplas et al., 2005).

It is a known fact that children's illness affects parents psychologically. If the disease is chronic, the degree of the effect becomes higher, and the course of the disease may be affected in a negative way (Whittemore et al., 2012). Studies investigating its effects on family have focused rather on mothers. It has been stated that these mothers are more depressive and neurotic than mothers of healthy children (Carter, 2014; Fonseca et al., 2013; Mastroyannopoulou et al., 1997).

Not only how effective the parent psychopathology is in the formation, continuation or exacerbation of GERD is not clear but it is also difficult to detect this relation (Lifschitz, 2011). Karacetin et al. (Karacetin et al., 2011) investigated this relation in their study. According to the authors, the psychological condition

of mothers of children diagnosed with GERD should be looked into too. This way, negative feeding habits that aggravate the disease can be avoided. For example, a study argued that feeding with big portions may increase the frequency of lower esophageal sphincter relaxation, also increasing regurgitation (Moukarzel et al., 2007).

It is aimed with this research, in this area investigated not much in the literature, to see whether the GERD/parental anxiety-and-depression relationship at early ages (2-36 months) shown by Karacetin et al. covers preschool period (3-7 ages), and to trace the obsessive-compulsive symptoms among the mothers. This seems to be the first study that applies to this age group with relation to the subject. The hypothesis is that mothers of children diagnosed with GERD have anxiety, depression and obsessive-compulsive symptoms more frequently.

METHODS

To conduct a study in case-control design, in addition to the case group composed of mothers of 50 children diagnosed with GERD, the mothers of 49 healthy children were taken as the control group. The GERD diagnosis was made according to the story and/or based on 24-hour pH monitoring. Between September 2019- march 2020, within the first month of each GERD diagnosis, the surveys were gathered. The number of cases in the time during the study period determined the sample size. The exclusion criteria were psychomotor retardation and a non-GERD physical condition in children. Mothers in the control group were picked from the healthy children polyclinic of the same hospital. Mothers of both groups were matched in terms of age, socio-economic and educational status. The study protocol was approved by the ethical committee of Yeditepe University Hospital.

The groups were matched according to age and educational status. The scales used in the study are Hospital Anxiety and Depression Scale and Maudsley Obsessive-Compulsive Inventory. Using chi-square, independent t-test and univariate analyses, both groups are compared with each other to find out whether there was a link between children's GERD and mothers' psychopathology.

Mothers of 50 children diagnosed with GERD were asked to complete a Socio-demographic Form (involving an appendix that investigates the feeding attitudes), the Maudsley Obsessive Compulsive Inventory (MOCI), and Hospital Anxiety and Depression Scale (HADS). As the control group, mothers of 49 children at the same age range who were monitored at the healthy children polyclinic and had no complaints and diagnosis. The psychomotor developments of the children in both groups were normal.

The studies assessing mothers' anxiety and depression levels in the literature was reviewed by the researchers, and a suitable socio-demographic interview form was prepared. An additional form consist of 3 questions about feeding patterns that are "food refusal", "mother's regarding the child's feeding as insufficient" and "forced feeding" were included. These questions are derived from a similar study made by Karecetin et al (Karacetin et al., 2011). As they remarked, food refusal is defined as spitting out food, gagging, or dawdling (Lindberg et al., 1994). These forms were given to the both groups.

Maudsley Obsessive Compulsive Inventory (MOCI)

Developed by Hodgson and Rachman (Hodgson & Rachman, 1977), the scale aims to investigate the level and type of the obsessive-compulsive symptoms. The scale is composed of checking, cleaning, slowness, doubting and rumination subscales. Each item purports to be a true/false question in the scale. Scores that can be obtained from the scale vary between 0 and 37, and higher scores indicate the increase in obsessive-compulsive symptoms. It was shown in the study that MOCI is valid and reliable for research and clinic purposes in measuring the type and prevalence of obsessive-compulsive complaints among normal and psychiatric samples in Turkey (Erol & Savasir, 1988).

Hospital Anxiety and Depression Scale

It is a 4-point Likert type scale developed by Zigmond and Snaith (Zigmond & Snaith, 1983) to determine the risk of anxiety and depression in the patient and measure its level and severity change. It is composed of 14 questions; odd numbers measure the anxiety, even numbers measure the depression. Turkish validity and reliability studies of the form were performed (Aydemir, 2009). It has subscales of anxiety (HAD-A) and depression (HAD-D). As a result of the study performed in Turkey, the cutoff score was found to be 10/11 for the anxiety subscale, 7/8 for the depression subscale. Accordingly, those who scored higher than these numbers are considered to be at risk. The lowest and highest scores which patients can obtain from both subscales are 0 and 21.

Statistical analysis

Chi-square analysis was used to calculate the relationships between the variables in the categorical structure. All scale scores' compliance with normal distribution was tested with Shapiro-Wilk test, and the distribution was found to be compliant with normal distribution. The internal consistency between the items of MOCI and (HAD-A)\(HAD-D) was evaluated with Cronbach's Alpha coefficient. Independent Samples t-test was used since data were distributed

parametrically in both groups. To see predictability between the feeding attitude and mothers' possible psychopathologies, if univariate analyses results statistically make sense, binary logistic regression is planned. The statistical significance level was considered to be $p \leq 0.05$ and SPSS (ver. 18) software was used for calculations.

RESULTS

In the study group, there were 50 mothers whose age range/average was 27-40/32.1 while the control group was composed of 49 mothers whose age range/average was 28-40/33.2. There was no significant difference between the two groups according to age, educational and social status (Table 1). The same values for the children were found to be 3-7/4.5 for the study group (31 males, 19 females) and 3-7/4.7 for the control group (32 males, 17 females). These values did not present a statistically significant difference in terms of both age (p=0.332) and gender (p=0.736).

Table 1: Characteristics of the mothers of GERD children and the mothers of the control group

Sociodemographic characteristics of the mothers	Case group	Control group	p
age	32.1 ± 3.2	33.2 ± 3.2	0.36
education			
primary and secondary school	12 (24%)	15 (30.6%)	
high school	21 (42%)	19 (38.8%)	
university	17 (34%)	15 (30.6%)	0.76
Marital status			
married	41 (82%)	41 (83.7%)	
single	9 (18%)	8 (16.3%)	0.82

GERD: Gastroesophageal Reflux Disease., The case group includes the children with gastroesophageal reflux disease.

The level of significance is set at P<0.05

Cronbach's Alpha coefficient was found to be 0.790 for anxiety, 0.742 for depression and 0.791 for Maudsley. These results show that the answers given to the scales had internal reliability.

Both anxiety and depression scores of the mothers in the study group were found to be significantly higher than those of the control group. In addition, there was no significant difference between the obsessive-compulsive scores (Table 2).

Table 2: Anxiety, depression and obsessive compulsive traits assesment of the case and control groups

	Case group			Control group			
	M	SD	SE of M	M	SD	SE of M	P
HAD -A	9.6	4.33	0.61	7.67	3.79	0.54	**0.02**
HAD-D	8	4.11	0.58	6.10	3.32	0.47	**0.01**
MOCI	11.14	5.09	0.71	9.67	5,.06	0.72	0.15

Independent t test is used, M: mean, SE:standard deviation, SE of M: standard error of the mean, HAD –A: Hospital Anxiety and Depression Scale- Anxiety Subscale, HAD –D: Hospital Anxiety and Depression Scale- Depression Subscale. MOCI: Maudsley Obsessive Compulsive Inventory.

Results of some items in all three scales exhibit statistically significant differences in both groups Table 3).

Table 3: The scale items which are found significanty different between the groups

	Case group			Control group			
	M	SD	SE of M	M	SD	SE of M	P
Anxiety							
"I feel tense or wound up"	1.68	0.95	0.13	1.14	0.70	0.10	**0.02**
"I get a sort of frightened feeling like butterflies in the stomach"	1.38	0.85	0.12	0.91	0.53	0.07	**0.03**
Depression							
"I still enjoy the things I used to enjoy"	1.38	1.08	0.15	0.81	0.63	0.09	**0.00**
"I can laugh and see the funny side of things"	0.90	0.95	0.13	0.40	0.60	0.08	**0.00**
"I feel as if I am slowed down"	1.56	0.88	0.12	1.22	0.62	0.08	**0.03**
Obsession/Compulsion							
"I'm often late because I can't seem to get through everything on time"	0.36	0.48	0.06	0.18	0.39	0.05	**0.03**
"Neither of my parents was very strict during my childhood"	0.20	0.40	0.05	0.42	0.49	0.07	**0.02**

Independent t test is used, M: mean, SE:standard deviation, SE of M: standard error of the mean

The answers given to all three questions about the feeding patterns exhibit a significant difference between the groups (Table 4). The factors that produced P values of <0.05 in univariate analyses between each of the feeding patterns (as a dependent variable), mother's psychopathology(as a random variable) and case/control groups (as a fixed variable), were meant to be assessed by binary logistic regression analysis. Only two of them passed the quote. The one is "mother's regarding feeding as insufficient" and "mother's anxiety", the other is "forced feeding" and "mother's depression". Despite found statistically meaningful in univariete analyses(p=0,04, P=0,03), they reveal no statistically important predictability in binary logistic regression.

Table 4: Some feeding patterns among the children of the mothers from both groups

Feeding patterns	Case group	Control group	p	x^2
Food refusal	27 (54%)	12 (24.4%)	**0.00**	6. 59
Mother's regarding the child's feeding as insufficient	31(62%)	17(34.6%)	**0.00**	7. 38
Forced feeding	27(54%)	11(22.4%)	**0.00**	10. 41

Chi-square test is used.

Table 5 shows a chi-square test comparing two groups according to HAM-A and HAM-D cut-off points. Anxiety "tendency" (we couldn't use the term "diagnosis" because no in depth psychiatric evaluation is performed) was statistically higher in the case group(p=0,09). But It is statistically indifferent as in the case of depression (p=0,57).

Table 5: Anxiety, depression assesment of the case and control groups according to cut-off points for the scales.

	Anxiety		p	x^2	Depression		p	x^2
	cut-off				cut-off			
	above	below			above	below		
case	30 (61.2%)	19 (38.8%)	0.09	6.91	31 (62%)	19 (38%)	0.57	3.63
control	17 (34.7%)	32 (65.3%)			21 (42.9%)	28 (57.1%)		

DISCUSSION

Being healthy is the basic factor of maintaining the life. Even though adults having a unhealthy child are provided with the best living conditions, they may not benefit from them (Mu, 2005). The most effective reason is the disease psychologically traumatizing the family. A physical disease is a life crisis. It poses a threat against the physiological and psychological integrity of the individual. This creates more parental anxieties if the ill one is a little child. Parents have concerns about how long this condition will continue and when their child will go back to his/her healthy life. If the answer to this question is a few

days, weeks or months, it is considered to be a rather tolerable and bearable condition (Mastroyannopoulou et al., 1997).

As for the literature related to the study subject, moods of the parents of children who have feeding/eating difficulty has been investigated relatively less (Garro et al., 2005). The results of our controlled research which is the first to include the mothers of preschool age (3-7 yrs) children as far as known are complaint with the results of the study by Karacetin et al. who found higher anxiety and depression scores among GERD infant's mothers than other mothers (Karacetin et al., 2011). In Turkey, may be less than the past, children who are very appetent and weigh above the upper normal limits are culturally considered to be healthy (Unlu et al., 2006). Therefore, we see lots of mothers around us who may say "he/she doesn't eat anything!" for a child even with a normal appetite. So, the relationship between the child diagnosed with GERD and the mother "holding responsible herself" for the condition may be a complex one. A study in which the diagnosed and undiagnosed groups were compared and a conflicted relationship was defined (Neu et al., 2014); and another study focusing on the stress laid on mothers by the risk of observing developmental delays in GERD diagnosed babies and children (Thoyre, 1994) support this observation of ours. In a study investigating the relationship between baby and mother in the context of reflux, stress and disappointment at high degrees were detected among mothers of babies with reflux especially during meal times (Dellert et al., 1993). There are also studies that emphasize not acquiring the habit of age-appropriate normal feeding, swallowing problems and mother-baby relationship problems related to the formation of GERD (Mathisen et al., 1999), as well as maternal-postnatal depression and anxiety (Harris & Bohane, 1994). Hence, the psychopathology of the mother beside the child's should not be ignored. Because the coexistence of organic and psychological factors in the formation of GERD requires both must be addressed together in the treatment (Chatoor, 2002; Hughes & Papaioannou, 2018). It has been stated in previous researches conducted on the adult patients diagnosed with GERD that psychopathological factors play a role in the formation of the disorder or the deterioration of the symptoms (Matsuki et al., 2013; Mengatto et al., 2013; Yang et al., 2015).

For the results related to the feeding attitudes, the differences observed between the two groups showed parallelism with previous studies (Karacetin et al., 2011; Williams et al., 2009). The definition of refusal to eat which is the most frequent symptom of GERD may differ according to the studies. In our study, refusal to eat was found to be closing mouth strictly, spitting the food or gagging the food out as in the study by Karacetin et al.; however, this is not a definition on which there is a consensus. Just as there are studies that define it as loss of

appetite (Staiano, 2003), there are also those that define it as the existence of a precise refusal enough to hinder development (Field et al., 2003). Beside several studies associating the refusal to eat with GERD (Mathisen et al., 1999; Nelson et al., 1998), the number studies that associates it with the mother psychopathology remains low.

Another interesting and new finding is that the feeding pattern which has been mentioned by mothers in almost all studies may not be *happening* actually. A research based on the observations during the meal time drew attention the difference between the things which mothers said and the things which they said they do (H. J. Bergmeier et al., 2015). One of the most "hidden" patterns, force-feeding has a strong relationship with non-organic refusal to eat, also according to the results obtained by us (H. Bergmeier et al., 2015; Levy et al., 2009). We think that one of the important diagnostic tips for non-organic refusal to eat is force-feeding. Unlike our study and the study by Lindberg et al. (Lindberg et al., 1994), Karacetin et al. (Karacetin et al., 2011) and Coulthard et al. (Coulthard & Harris, 2003) did not find any relationship. Another remarkable emphasize is again shown by the study of Karacetin et al.; according to the authors, the force-feeding behavior exhibited within the scope of insecure attachment may cause children to refuse to eat in future.

The relatively high level of anxiety among GERD mothers, in accordance with our predictions, is compliant with the results of a study in which it was examined as stress (Shepherd et al., 1987) and the results of another study that focused on the mothers of babies at the age of 3 and below (Karacetin et al., 2011). Mothers' concern about "feeding their children well" is a fact observed in all cultures (Wright et al., 2006). It would be certainly a fault to interpret this sensitivity, which can be said to be specific to the species and even the gender, as an anxiety disorder. Above all, it would not be surprising to see the traces of anxiety in the attitudes of a mother of a child diagnosed with GERD toward the feeding issue. However, considering this challenging relationship as an interactive, inter-growing problem rather than accepting it as a linear cause and effect relation may enrich the treatment options of clinicians. Therefore, the anxiety scores of the mothers in the study group higher than those in the control group do not indicate a psychiatric disorder but a probability.

When taking a closer look at the depression among the mothers in the study group, the results confirming our hypothesis seems to be compliant with other studies (Barnett et al., 1993; Harris & Bohane, 1994; Karacetin et al., 2011). Depressive mothers may not be ensuring that the meal time is enjoyable and peaceful. Moreover, they may be associating the problems their children are experiencing with the lack of their own motherhood skills. Hence, as in the

chicken and egg problem, refusal to eat may be a subconscious weapon of the child with GERD who establish a conflicting communication with the "unhappy" and "lacking" mother(Ballarotto et al., 2021; Santona et al., 2015). These psychoanalytic assumptions should be confirmed by well-designed, scientific studies.

Both study and control group mothers are retrieved from the institute in which we are currently workin. It is a private foundation hospital, not a state hospital. Therefore our patients usually belong to middle-upper socioeconomic status. So, it may not reflect the norms of the society and this condition may effect the generalizability of results. Furthermore, because data were collected cross-sectionally, we cannot predict how anxious and depressive mothers in our study group will react in GERD free life, after treatment. Are they relieved or will continue to worry about the feeding in general terms?

This study is, as far as we are concerned, the first one to cover the mothers of children at the age between 3 and 7, but its biggest drawback is that it focuses only on the mother psychopathology and do not assess children diagnosed with GERD from this aspect. In other words, we are able to make assumptions only about the mother in a mother-child relationship. Another deficiency we plan to fulfill through a newly designed study is that the data we have is cross-sectional. Would there be any recovery in the symptoms of children with GERD 6 months and 1 year later if we psychiatrically monitored the mother who volunteered for it? Giving a positive answer to this question may be the pioneer of a major change in the protocols of GERD treatment.

These findings are of clinical interest that, not just GERD children' mothers may be suffering from anxiety and depression, moreover, children having maladaptive feeding behavior implicated above should be evaluated in terms of GERD and maternal psychopathology. The main point here is the interaction between mother and child on the basis of "asynchronous" feeding patterns should attract the clinician's attention before negative reinforcement may develop which may possibly worsen GERD prognosis. Such an intervention should include a multidisciplinary approach from, at least, a pediatric gastroenterologist and a child psychiatrists.

Competing interests

The authors declare that they have no competing interests.

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Chapter 8

Intermittent Fasting Modulates Age-Dependent Morphological and Histological Hepatic Changes on Liver Tissue in Wistar Rats

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Abstract

Background: Intermittent fasting (IF) plays an essential role in improving age-related cellular degenerative alterations and metabolic diseases.

Aim: This study aimed to evaluate the protective effects of IF on aged-related liver degenerations in Wistar albino rats.

Material and Methods: In this study, twelve rats were divided into two groups: the Nonfasting Group (12 months) and the Fasting Group (12 months with IF for 35 days). The food access interval of the Fasting group was between 09:00 am and 15:00 pm and their access to food was restricted for 18 hours. At the end of this experiment, all liver sections of groups were stained with H&E and Masson trichrome, and all stained slides were evaluated for histological examination with light microscopy.

Results: The results showed that there was a significant increase in inflammations (lobular and portal), spotty necrosis, and ballooning degeneration in the Nonfasting group compared with the Fasting group which had a significant decrease. There was a significant increase in the density of collagen fibers noticed for the Nonfasting group compared to the Fasting group.

Conclusion: The anti-inflammatory and antioxidant effects of IF morphological changes may be beneficial in the Fasting group through modulating autophagy in aged liver cells.

Keywords: Aging, inflammation, intermitted fasting, liver, histopathology

Introduction

Global average of life expectancy continues to rise. Aging is considered one of the major risk factors for the development of metabolic and renal disease [1]. As aging increases the likelihood of frailty, which encompasses metabolic, musculoskeletal, and cognitive deficits, there is a need for effective anti-aging treatments [2]. Caloric restriction or agents that mimic caloric restriction may improve survival and delay age-related diseases in mammals and non-mammal organisms [3]. Intermittent fasting (IF) is one of the methods of energy deprivation which is distinct from caloric restriction[4]. Unlike caloric restriction, the energy intake through IF does not need to be limited; inturn, the frequency of food intake is controlled [5]. It is reported that intermittent or periodic fasting protects and delays the onset of metabolic and age-related diseases such as diabetes, heart disease, neurodegeneration, obesity, hypertension, cancer, asthma, and rheumatoid arthritis in rodents and human [6]. It increases longevity and minimizes the side effects caused by chronic dietary regimens [7]. IF improves myocardial tolerance and protects the rat heart from ischemic injury, in addition to reducing post-MI (myocardial infarction) cardiac remodeling, most likely via antiapoptotic and antiinflammatory effects. [6]. In addition, IF can reduce the heart rate and blood pressure and can improve cardiac diastolic parameters. It is also known to extend the lifespan of mice and rats. Aging represents the collective changes in all organisms over time, which encompass physical, psychological, and social changes. Age-related diseases include diabetes, cancer, arthritis, dementia, vascular diseases, obesity, and metabolic syndrome. Dietary interventions such as prolonged calorie restriction and intermittent fasting provide health benefits, including a reduction in the inflammatory burden and regulation of energy metabolism [8,9]. Time-restricted feeding (TRF; also referred to as intermittent fasting) confines the period during which food is consumed to specific hours of the day (typically a 6–8 h window) [10]. TRF or IF both refer to a variety of dietary paradigms, each of which incorporates short periods of fasting ranging from hours to a whole day, with many options therein. It is well established in model organisms that IF such as caloric restriction or protein restriction, enhances health and lifespan [8]. But IF is used a lot in clinics because of age-related diseases that affect the whole body. It should be used in a controlled way for each organ type.

The liver is a critical organ that supports digestion, metabolism, immunity, detoxification, vitamin storage, and hormone signaling [11]. Nevertheless, the relationship between aging and the development of liver diseases remains elusive. In fact, although prolonged fasting on adult rodents and humans delays the onset of the disease and increases longevity, whether prolonged fasting could exert adverse effects in old organisms remains incompletely understood. Many studies

in experimental models and humans have been conducted to find the link between oxidative stress and aging at the molecular and cellular levels and revealed that in conditions of metabolic syndrome (MS), oxidative stress could accelerate aging [9]. Moreover, a considerable amount of evidence points to the process of immunosenescence as the major contributor to the chronic basal inflammation associated with aged related inflammation and to increased oxidative stress [12]. The biology of aging is not well understood, and it is still not clear if oxidative stress is a key regulator of aging and diseases that come with age. This is an issue that needs to be resolved.

One of the most remarkable effects of IF might be healthy weight loss, but recent studies have also found many other valuable effects at the tissue level [4]. IF in animals and humans has been considered one of the dietary restriction methods that has been confirmed to possess antioxidant and anti-inflammatory properties [2]. Moreover, IF has been demonstrated to lower fasted insulin levels, improve glucose tolerance, and lower blood cholesterol, although its underlying molecular mechanisms are not fully understood yet. IF can be effective in reducing metabolic disorders and age-related diseases. However, there remain questions about the effects of fasting regarding the age at which fasting begins, the fasting models, and the mechanisms involved. Because the liver is so important for controlling metabolism and digestion, the goal of this study was to look at how 18-h IF changed the liver tissue of rats over the course of 5 weeks. The present study purposed to examine the effects of a somewhat more pre-clinically applicable and adoptable IF regimen on the rat liver, every day IF for thirty-five days, one frailty in middle-aged rats

Materials and methods

Animals and Housing

The male *Wistar* rats (12-month old) were used as a model organism in the study. The maximal life span of the male *Wistar* rats is about 32–34 months, while the mean life span is about 24 months [13]. Thus, the 12-month-old rats used in the present study were middle-agedanimals. These old rats didn't have a high risk of dying and didn't seem weak, but they did have more lipofuscin inside their cells than 3-month-old *Wistar* rats, which is a sign of cellular senescence [14]. In order not to subject the rats to a new tension in a short time period, the data of the rats that were not composed or were lost during an experiment were not repeated. Therefore, the number of rats per age is not continual in all *in vivo* studies and may change with each age. Animals were housed in climate-controlled quarters with a 12-h light cycle. Animals were handled according to the European Union

laws (2010/63/EU) and following the Turkish regulations for the use of laboratory animals. Our study was carried out with the approval of the Ethics Committee (approval number: 2021/05) from the Saki Yenilli Experimental Animal Production and Practice Laboratory. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Experimental design

In this study, *Wistar* albino male rats were divided into two groups, as the Non-fasting group (12-month-old, n=6) and the Fasting group (12-month-old, n=6). For 35 days, rats in the study's experimental group (Fasting) were subjected to IF. While the rats in the experimental group could always drink water, their access to food was limited to 18 hours, and they could only feed for 6 hours. The experimental group's food access period was determined to be between 9:00 am. and 3:00 pm [15]. The control (Non-fasting) group was allowed access to water and food for 24 hours. The animals were fed a standard rodent diet on an ad libitum basis. The body weight of the animals, the feed, and the consumed water were followed for 35 days. The animals' daily body weight measurements as well as their intake of food and water consumed were tracked throughout the intermittent fasting program. There was no significant reduction in the body weight of the animals ($p > 0.05$). The animals in the experimental and control groups were treated with ether therapy and killed one day after the application period had ended. Liver samples were excised, surgically taken, and processed for histological study. After, the tissues were suspended in buffered 10% formaldehyde for fixation preparatory to histological processing.

Histopathological evaluation

The liver tissue biopsies were fixed with buffered 10% formaldehyde for about 72 hours for all histological analysis. After tissue procession, the tissue samples were embedded in paraffin blocks, and the all blocks were cut into 5 μm thickness [16]. The tissue sections were stained with H&E for histological evaluation, while the Masson Trichrome staining was used to assess collagen deposition as a marker of fibrosis. Hepatic tissue sections of all groups were studied, and the following changes were evaluated. For histopathological evaluation, an average of 6–10 areas were evaluated by random sampling for each animal in all groups. The evaluation of hepatic alterations was estimated by a semi-quantitative method as follows according to the number of lesions observed in examined areas. According to Thoolen et al.[17], histopathological scoring research was conducted. The evaluation was represented as the sum of the individual grades of 0 (−, none), 1 (+, minimum), 2 (++, mild), 3 (+++, moderate),

and 4 (++++, severe) for each of the following liver parameters: spotty necrosis, lobular and portal inflammation, and ballooning degeneration of hepatocytes [18]. In all microscopic analyses, the histopathological changes of the study were carried out by two independent researchers who were blinded to the randomization scheme. All findings were confirmed while excluding artifacts through comparison with histochemical slides. The slides were examined under a light microscope (Zeiss Axioskop 2 Trinocular Brightfield) using a camera (Digital Camera Axiocam 208 color (Oberkochen, Germany) and microscope imaging systems (Axiocam ZEN 3.0 Blue edition core imaging software).

Statistical Analysis

Statistical evaluations and graph plots of the results were made using GraphPad Prism 8.01 (GraphPad, USA). The data were analyzed using an unpaired t-test, and the significance levels between the Nonfasting and the Fasting groups were stated as $p \leq 0.05$ * and ** $p \leq 0.001$. Results are presented as mean ± SEM (standard error of the mean).

Results

Light microscopic results

H&E evaluation

In the H&E results, we found that congested central vessels and dilated sinusoids were seen intensely in the Nonfasting group. It was noticed that most hepatocytes around the central veins had dense nuclei, dense eosinophilic cytoplasm, and vacuolated cytoplasm. Some hepatocytes surrounding the portal area appeared also with dense nuclei. There was an increase in the density of Kupffer cells in the sinusoidal spaces between the hepatic cords. Dilated portal vessels surrounded by inflammatory cell infiltrations were another finding detected. Some hepatocytes around the portal area also had dense nuclei (Fig. 1A). The H&E stained liver sections of Fasting group showed nearly the normal hepatic structure. The hepatocytes radiated like cords from the central veins to the periphery of the lobules that contained portal areas. The plates of hepatocytes were separated by blood sinusoids. Hepatocytes showed eosinophilic granular cytoplasm with central vesicular nuclei and prominent nucleoli. Some hepatocytes had two nuclei. The Kupffer cells were seen hanging in the blood sinusoids. The portal areas contained branches of hepatic arteries, portal veins, and bile ducts (Fig.1B).

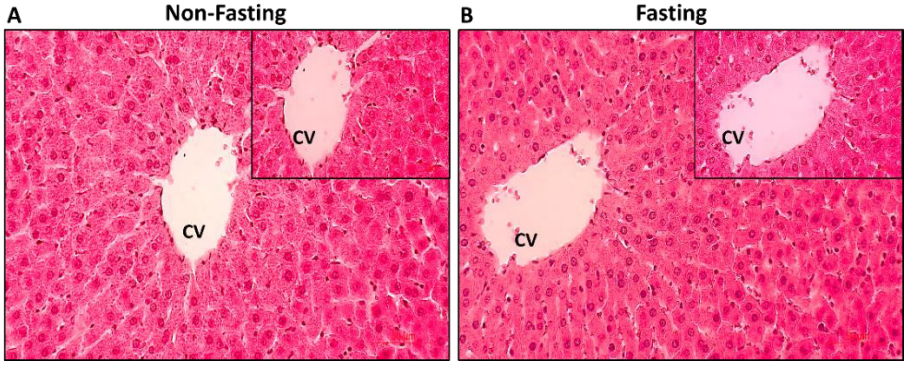

Figure 1. Photomicrographs of the rat liver sections in Control (Nonfasting) and Experimental (Fasting) group Figure 1A: Nonfasting group showing inflammation in the sinusoidal areas around CV. Figure 1B: Fasting group showing inflammation is reduced in the sinusoidal areas around CV. CV: Central vein, H&E, Scale bar: 20 µm.

Histological examinations and statistical results of pathological parameters are seen in Fig.2 and Fig.3. Nonfasting rats showed significantly pathological changes, lobular inflammation, including degeneration of hepatocytes and spotty necrosis (Fig.2A and Fig.2B). Degenerative and necrotic modifications were significantly increased in the hepatic cells around portal area (Fig.3A and Fig.3B). Moreover, in the Nonfasting group, focal aggregations of lymphocytes and ballooning degeneration were also significantly increased around periportal areas (Fig.3C and Fig.3D). However, in the Fasting group treated (Fig.2C and Fig.2D), IF significantly decreased spotty necrosis, lobular inflammation, periportal inflammation and ballooning degeneration, improved the liver histological appearance compared to the Nonfasting group (Fig.3A, Fig.3B, Fig.3C and Fig.3D). Besides, rat liver tissue micrographs revealed normal hepatic cell and central vein architecture and normal blood sinusoids in the Fasting group.

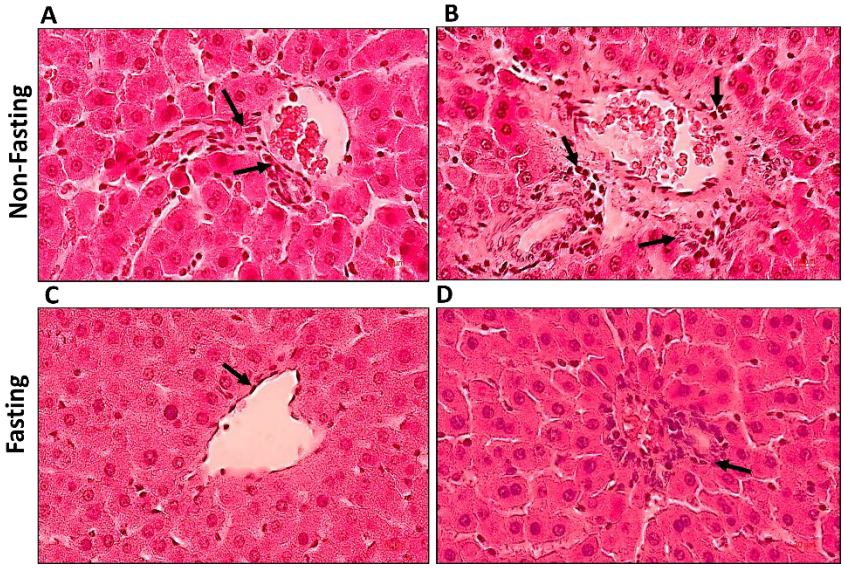

Figure 2. Photomicrograph of the liver tissues in Control (Nonfasting) and Experimental (Fasting) group. Figure 2A and Figure 2B: Nonfasting group showing moderate hepatocellular spotty necrosis in periportal and pericentral areas with lymphatic infiltration, mononuclear inflammatory cell aggregation with disorganization of hepatic cords (black arrows). Figure 2C and Figure 2D: Normal histological architecture of the liver and normal hepatic cords and hepatocytes were observed in the fasting group (black arrows). H&E, Scale bar: 20 µm.

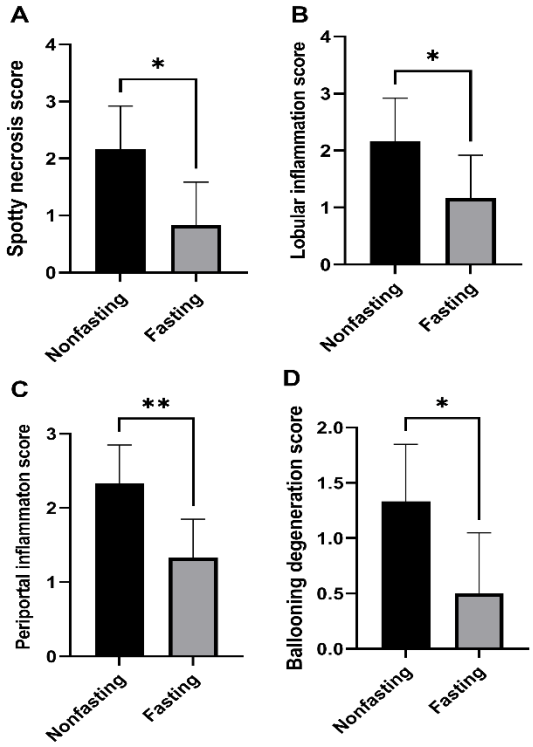

Figure 3. Histological scores of severities obtained for liver in the Nonfasting and the Fasting groups with 35 days. Figure 3A: Bar chart showing cumulative spotty necrosis scores for liver in all groups. Figure 3B: Bar chart showing cumulative lobular inflammation scores for liver in all groups. Figure 3C: Bar chart showing cumulative periportal inflammation scores for liver in all groups. Figure 3D: Bar chart showing cumulative ballooning degeneration scores for liver in all groups. Values are presented as the mean ± standard error of the mean. (** ($P<0.01$); * ($P<0.05$)).

Masson's trichrome staining evaluation

Histological sections of the liver from each group were stained with Masson trichrome (collagen content presented with blue color). Masson's trichrome-stained sections of the Nonfasting group revealed an apparent increase in collagen fibers deposition around the portal tracts. An increase of collagen fibers around blood sinusoids was also noticed (Fig.4A and 4B). Meanwhile, in the Fasting group, an increase of collagen fibers around the portal tracts and central vein, was not prominent when compared with the Nonfasting group (Fig.4C and 4D).

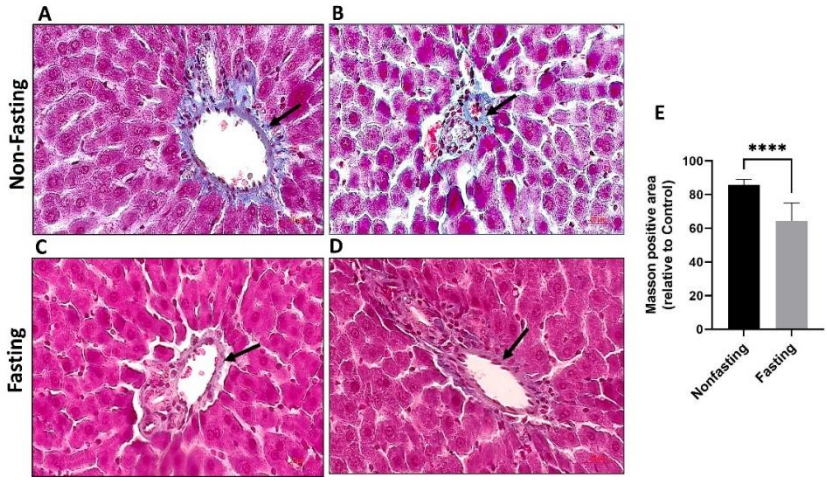

Figure 4. The Masson trichrome stain was used to color the liver cells in this photomicrograph. Figure 4A: Nonfasting group demonstrated marked collagenous fibrous bridging with excessive collagen fiber deposition from portal to central regions and from portal to central regions (black arrows). Figure 4B: Nonfasting group demonstrated marked collagenous fibrous bridging with excessive collagen fiber deposition from portal to central regions and from portal to central regions (black arrows). Figure 4C: The amount of collagen fibers deposited and distributed from the portal to the central areas was significantly reduced in the fasting group (black arrows). Figure 4D: Fasting group showing normal collagen fibers spreading around the portal area (black arrows). The fasting group exhibited normal collagen fiber distribution around the portal area (black arrows). Figure 4E. Quantification of the Masson's trichrome-positive area demonstrating a remarkable ameliorative effect of intermittent fasting and a significant decline in collagen deposition. Scale bar: 20 µm. Data are expressed as mean ± SEM, n = 6, ****P< 0.001.

Discussion

Intermittent fasting is one of the energy deprivation methods involved in the reorganization and improvement of various metabolic parameters and is a type of dietary restriction [10,19]. Various forms of IF cause changes in fuel selection, increase the efficiency of metabolism, regulate repair mechanisms, stimulate autophagy, reduce oxidative stress, and prevent both metabolic illnesses and aging [20]. Studies have been conducted in animal models and human trials revealing that intermittent fasting is effective in preventing or delaying the onset of metabolic and age-related diseases such as diabetes, obesity, cancer, and

hypertension [15,21]. In addition, debates about the age at which fasting is practiced and its effects related to this age continue to exist [22].

Aging is a condition in which physiological functions decrease, accompanying the accumulation of oxidative damage and causing the deterioration of homeostasis [23]. Although the aging process is not a disease, it is an important risk factor for chronic metabolic diseases [3]. Reducing lifelong food intake affects aging and lifespan [24]. Although IF lasting from 16 to 48 hours is one of the preferred fasting practices, there is some debate about its possible adverse effects. However, according to recent research, IF may be a safe and highly effective application for promoting healthy metabolism and delaying aging [25]. One of the prominent effects of IF is healthy weight loss, but recent studies have revealed many other beneficial effects at the cellular level. Because there is a calorie restriction at the specified time intervals, blood sugar and insulin levels gradually decrease. Ultimately, this may help prevent insulin resistance that occurs because of metabolic diseases [26]. Age-related liver changes that significantly affect liver morphology and oxidative capacity have been reported [27]. Since there is a decrease in autophagy due to aging, damaged organelles can accumulate in aged liver tissues. Intermittent fasting and its balanced anti-aging effect work by turning on autophagy and getting rid of unwanted, damaged, or extra cell organelles and structures. This is done by getting rid of unwanted, damaged, or extra cell organelles and structures. Thus, IF-induced autophagy can recognize and selectively degrade altered cell organelles accumulated in aged cells, playing a role in antiaging mechanisms of caloric restriction. Studies have reported that IF is the only established intervention that significantly increases the mean and maximum lifespan in rodents, keeps physiological processes in a youthful state, and delays many age-related diseases [28]. One study found that IF transiently increased autophagy markers in the liver in intermittent fasting mice fed a meal or high-fat diet [29]. In another study, it was found that cellular and physiological responses to fasting depended on age, and that older animals responded better to fasting [22].

Hafez et al. (2022) studied the effects of IF for three months on the aged liver in 1-month and 15-month-old male albino rats, with a significant decrease in autophagy markers, liver damage, oxidative stress, and a significant increase in inflammatory markers in liver samples of non-fasting rats (15-month-old). However, in the histopathological evaluation results, hepatic vacuolations, lymphocytic filtration, a significant increase in the surface area fraction of collagen fibers, and occlusion of both central and portal vessels were detected. 15-month-old rats that underwent IF for three months significantly reduced previous histopathological changes compared to non-fasting rats [30]. In this study,

we investigated the effects of intermittent fasting for 35 days on the liver tissues in the middle-aged rats. According to our results, we detected significant spotty necrosis in liver tissues, periportal and lobular inflammation, together with balloon degeneration of hepatocytes in the control group (Fig.3), that did not apply intermittent fasting and evaluated them together with histopathological scoring. However, a significant improvement was observed in the changes detected in liver tissues in the group that fasted for 35 days. Our results are consistent with the findings of the study by Hafez et al [30]. The intermittent fasting period we applied in our study had a shorter duration compared to the study of Hafez et al. In addition, the rats we used in the intermittent fasting model were in the middle age group (12 months). These differences in our study have shown that intermittent fasting may be effective in the curative and retarding role of senility in liver damage in the middle-aged group in a shorter time compared to previous studies. These findings indicated the importance of intermittent fasting's regulating and anti-aging effects on liver metabolism in reducing cellular damage that may occur in the liver tissue in early aging. In the results of Masson's trichrome staining, there was an increase in the density of collagen fibers in the non-fasting group and a decrease in the Fasting group because of the regulatory effect of IF on liver metabolism. This finding is in line with previous studies suggesting a higher accumulation of fibrosis in aged rats and linking this to changes in the inflammatory response [30,31]. In a recently published study, we used Support Vector Machine (SVM) and Linear Discriminant Analysis (LDA) algorithms built on infrared spectrochemical data to look at how intermittent fasting changes the biomolecules in rat liver tissue. In particular, the concentrations of lipids, proteins, and nucleic acids and the rate of phosphorylation of proteins were higher in the examined tissues of IF-treated rats. An increase in the liver (35% increase) was noted in the enhanced membrane dynamics results (Bw 2922/Bw 2955 bandwidth ratio) [32]. The study revealed significant changes in major metabolism-related biomolecules in the liver tissue studied. The findings are congruent with histopathological assessments on IF-induced modulations in the liver tissue of albino rats.

Conclusion

In summary, we concluded that intermittent fasting reduced damage to middle-aged liver tissue in a short period (35 days) involved in the aging and metabolic process. We represented that the middle-aged rats under intermittent fasting had significantly improved liver and reduced inflammation and necrosis in agreement with previous results. Taken together, these findings provide supportive insights into the histopathological changes induced by aging in the

middle-aged liver that could aid in understanding the pathogenesis of IF. More detailed research is needed to enlighten the effects of IF on liver metabolism and functions and the histological mechanisms that are effective here. Given the side effects and toxicity associated with using pharmaceutical interventions to prevent aging and age-related diseases, intermittent fasting may aid clinical treatments through relatively simple dietary interventions.

Author contributions statement

Taha Ceylani: Conceptualization, Funding acquisition, Investigation, Methodology, Writing –original draft, Writing –review &editing. **Hikmet Taner Teker**: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing–original draft, Writing–review &editing. **Isıl Eranıl:** Histopathological analysis, Histopathological interpretation, Writing – original draft, Writing–review & editing. **Fatma Yılmaz Ertürk:** Histopathological interpretation, Writing– review &editing. **Seda Keskin**: Histopathological analysis, Histopathological interpretation, Visualization, Writing–original draft, Writing – review &editing. All authors read and approved the final manuscript.

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Declarations

Ethics approval: This study was carried out with the approval of the Ethics Committee (approval number: 2021/05) from the Saki Yenilli Experimental Animal Production and Practice Laboratory.

Consent to participate: For this type of study, consent is not required.

Consent for publication: Consent for publication is not required in this study.

Conflict of interest: The authors report no conflict of interest.

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Chapter 9

The Impact of the Gut Microbiome Alterations in Psoriasis

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Abstract

The relationship between the gut and the skin, known as the gut-skin axis, plays a significant role in the development of psoriasis. The skin and gut are connected by a complex network of systems, including the crucial role played by microbiota. Patients with psoriasis have a weak gut barrier, so they are more likely to get diseases like irritable bowel syndrome that throw off their already delicate health balance. Researchers are working hard to find out what causes the gut barrier to break down in people with psoriasis and whether this could be a cause or effect of the disease. It has been proposed that the microbiota has a role in the pathophysiology of psoriasis. Despite tremendous breakthroughs in current biological therapy for psoriasis, there are still people who do not respond properly or who experience unpleasant consequences. The key to effective treatment should be personalized medicine. The goal of current scientific investigation is to find biomarkers that can forecast the emergence of negative side effects in psoriasis patients receiving biologic therapy. The aim of this section was to review the literature and determine the relationship between intestinal microbiota correlation with psoriasis and its pathophysiological process. We consider that the composition and activity of the gut microbiota may influence the efficacy and safety of the therapy and contribute also possible side effects.

Keywords: Psoriasis, microbiota, gut, skin, inflammation

Introduction

The microbiota of the human intestine consists of trillions of minute creatures, primarily bacteria. They have a vital role in food metabolism, the preservation of the structural integrity of the gut mucosal barrier, immunomodulation, and pathogen defense (Wen et al., 2023). Numerous factors, consisting as antibiotics, nutrition, cleanliness, stress, immunodeficiency, and hyperimmunity, might impact the composition of the gut microbiota. These variables may result in dysbiosis, which stimulates neurotransmitters. It can lead to the admission of metabolites into the bloodstream, systemic immunological dysregulation, and alterations in skin microbiome (Yu, Wang, Liu, & Guo, 2023). Numerous studies suggest that altered gut microbiota may be associated with some chronic diseases, such as skin disorders such as psoriasis, atopic dermatitis, hidradenitis suppurativa, and rosacea (Mina, 2023). In addition, it has been demonstrated that bacterial dysbiosis might exacerbate the inflammatory process of the skin.

Microbiota and Microbiome

Microbiota and microbiome are the names given to the community of microorganisms living in the human body. However, there are some significant differences between these two terms. Microbiota refers to the species, number, and diversity of microorganisms. The gut microbiota includes all the bacteria, viruses, fungi, and protozoa that live in our intestines. Each of these microorganisms has a different function and plays an important role in maintaining our gut health. The term "microbiome" is used to describe the community of microorganisms found on or within a host organism as well as the metabolites, genes, and enzymes produced by these microorganisms. The gut microbiome produces metabolites that play a role in breaking down food in our intestines, synthesizing vitamins, and regulating the immune system. The microbiota is just one component of the microbiome. While the microbiota forms the physical structure of the microbiome, the microbiome encompasses the functional aspects of the microbiota. Bacteria, fungus, and protozoa make up this defined microbiome, which has 150 times more DNA than the host. The human gut has tens of billions of symbiotic bacteria, including the niche microflora. Human colons have the most microbial variety on Earth (Jandhyala et al., 2015; Thursby & Juge, 2017). In the human gut, there are numerous bacteria of the classes Bifidobacterium, Bacteroides, Prevotella, Fusobacterium, Eubacterium, Peptococcus, Peptostreptococcus Ruminococcus, Escherichia, and Lactobacillus (Jandhyala et al., 2015). Approximately 30% of all GI tract microorganisms are Bacteroides alone. In healthy adults, Phyla, Firmicutes,

Bacteroidetes, Proteobacteria, and Actinobacteria are more prevalent (Sekirov, Russell, Antunes, & Finlay, 2010). When population density varies between species of different microbiota classes, it contributes to a variety of health-related complications. The microbiome also contributes to the host's innate and adaptive immune systems. Inflammation and autoimmune disorders are brought on by microbiome dysbiosis. Metabolic activities that are highly associated with host characteristics like age, nutrition, and environmental conditions are released by intestinal dysbiosis. The Human Microbiome Project started conducting studies to enumerate and define the human microbial flora in conjunction with the mechanistic discoveries of host-microbe interaction in 2007 (Moeller et al., 2016; Perler, Friedman, & Wu, 2023). Therefore, the gut microbiota has become one of the main targets for improving human health. Identification of diseases that may be related to microbiota may revolutionize the effective treatment of diseases whose course is known and for which there is no definitive treatment and many other drug-dependent diseases. Microbiome technologies are predicted to play an important role in today's functional medicine era, which could revolutionize the development of new drug discovery methods and accompanying diagnostics. Three distinct enterotypes are recognized in the human gut microbiota: Bacteroides, Prevotella and Ruminococcus (Jandhyala et al., 2015). Intestinal microbial enterotypes vary according to people with different dietary habits and drug intakes. The 16S rRNA gene of the human intestinal tract microflora is used in research on these diversity factors (Yoshida, Yamashita, & Hirata, 2018). Previous metagenomic studies have characterized the functional microbiome between American and Japanese individuals (Walker & Hoyles, 2023). Intestinal flora includes Lactobacillus, Bifidiobacteria, Peptostreptococci Propionibacteria and Enterococci (Thursby & Juge, 2017). The most important tasks of these microorganisms are to live commensally and preserve the intestine after secreting an antibiotic substance that prevents the growth of harmful microorganisms and maintains the necessary pH for the intestinal wall to form a protective barrier and provide an environment for microbes to shelter. Dysbiosis of the microbiome can lead to chronic inflammation and autoimmune diseases that develop because of disruption and damage to the intestinal barrier function in which an immune cascade is activated (Carding, Verbeke, Vipond, Corfe, & Owen, 2015; Perler et al., 2023).

Function and Importance of the Gut Microbiota in Psoriasis

The diversity of microbiota in the gut enables the breakdown of complex components of nutrition and the execution of many vital activities necessary for

metabolic and immune functions. The outer layer of the intestine secretes mucins to protect against pro-inflammatory compounds and uptake antigens. This is important in the long-term preservation of intestinal microbiota, intestinal structure, and enterocytes (Mina, 2023; Yoshida et al., 2018). As a result of this disruption of microbial balance, inflammatory diseases can emerge, or existing diseases can relapse. The results of previous studies support the notion that the microbiota is involved in every stage of growth and development related to inflammatory process disorders. Other studies show that imbalances in the composition, habitat, or number of gut microbiota tend to cause dysfunction in humans and are strictly interrelated (Guerreiro, Calado, Sousa, & Fonseca, 2018). A persistent inflammatory skin condition called psoriasis is brought on by the immune system's ineffective response. It causes the production of pro-inflammatory cytokines to increase (Pasquali, 2020). The condition frequently impacts multiple facets of life, greatly reducing its quality. According to studies, persons with psoriasis have a different gut microbiome than people who are healthy (Yu et al., 2023). People with different types of psoriasis (pustular vs. psoriasis vulgaris, for example) have different gut microbiota. The outcomes of studies looking at how changes in the gut flora may affect the progression of psoriasis are also quite encouraging (Buhaș et al., 2022). Many studies on the surface or skin microbiota have confirmed the high strains of Staphylococcus and Streptococcus (Damiani et al., 2020). Bacterial DNA has been isolated both locally and systemically in psoriasis patients, providing complete evidence that bacteria play a central role in psoriatic disease (Hsu, Fung, & Chen, 2020).

There is a recent strong trend to investigate what triggers the disruption of the intestinal barrier in patients with psoriasis and whether this is a cause or a consequence of the disease. In psoriasis, there is a characterized disturbing barrier dysfunction in both the skin and the gut. In psoriatic skin, this condition is often associated with the altered composition of the microbiota, increased antimicrobial peptide production, increased transepidermal water loss, and overall inflammation resulting in redness, thickening, and accelerated cell cycle in psoriatic lesions. In the gut of patients with psoriasis, the diseased condition is typically characterized by microbiota dysbiosis, lower production of short-chain fatty acids, impaired mucus layer, increased gut permeability, or decreased IgA secretion (Maciel-Fiuza et al., 2023; Mariusz Sikora et al., 2019; Wen et al., 2023; Yu et al., 2023). One contributing factor to the disrupted gut barrier is believed to be the systemic increase of cytokines such as IL-17 and TNFα (Kapoor, Gulati, Rani, & Gupta, 2022). Additionally, the overexpression of tight junctions in psoriatic lesions results in a defective skin barrier. This

condition is supported by the overexpression of occludin and zonulin (ZO-1) in acanthotic spinous cell layers and claudin-5,2 in the granular cell layer (Peltonen, Riehokainen, Pummi, & Peltonen, 2007). Furthermore, a study by Sikora et al. reported elevated serum levels of claudin-3 in patients with psoriasis, which is typically associated with epithelial tightness (Sikora et al., 2018). Moreover, patients with psoriasis have been found to have three times higher serum zonulin levels compared to healthy controls (Richetta et al., 2020). While reported studies suggest the potential use of serum zonulin as an indicator of intestinal mucosal barrier function (Ajamian, Steer, Rosella, & Gibson, 2019), the positive correlation between serum zonulin and serum lipopolysaccharide indicates disrupted intestinal barrier function, leading to bacterial translocation into the bloodstream (Richetta et al., 2020). The concentration of changing serum markers in psoriasis patients, such as claudin-3 or intestinal fatty acid-binding protein (I-FABP) concentration, could suggest the presence of intestinal barrier damage in these patients (M Sikora et al., 2019; Mariusz Sikora et al., 2019; Stehlikova, Kostovcik, et al., 2019). Interestingly, I-FABP levels have been positively correlated with increased body mass index (BMI), psoriasis area and severity index (PASI), and neutrophil-to-lymphocyte ratio (NLR), indicating that I-FABP levels are affected by intestinal integrity, obesity, disease severity, and systemic inflammation (Mariusz Sikora et al., 2019). Further investigation of other indicators of disrupted intestinal barrier in patients with psoriasis and their effects on disease pathogenesis is warranted.

While researching the effects of host-microbiota interactions on disease processes, many unresolved questions regarding the gut flora and psoriasis remain unclear. This is a vast field with numerous unanswered biological questions that could greatly enhance our understanding of human pathophysiology if they are answered. Researchers are turning to high-throughput sequencing methods and bioinformatics systems to better comprehend how the human microbiome impacts our health. The phylogenetic information of the microbiome can be obtained by identifying genes and the complex functions of these communities using a DNA sequencing approach. With the use of artificial intelligence, studies such as the ability of microbial composition to predict age can lead to a lot of predictability (Chen et al., 2018; Guerreiro et al., 2018; Knox, Forbes, Peterson, Van Domselaar, & Bernstein, 2019). Research on the effects of the gut microbiota on inflammatory diseases like psoriasis has increased in recent years, and researchers from various scientific fields are hopeful that these cutting-edge technologies will help

unlock the potential of the gut microbiota for personalized medicine development.

Gut Microbiome Changes in Psoriasis

All studies confirm the relationship between psoriasis and intestinal microbiota dysbiosis. Intestinal microbiota study of psoriatic patients clears abundance of *Prevotella copri.* A decrease in the genus Bacteroides and an increase in the number of Faecalibacterium, Akkermansia, and Ruminocuccus are also characteristic findings in the gut microbiome of psoriasis patients (Buhaș et al., 2022; Wen et al., 2023). The African pilot study found that Prevotella species predominately contribute to rheumatoid arthritis in the gut. Auto-reactive T cells activate innate immunity to react strongly to autoantigens, including arthritis-specific antigens. Consequently, these T cell subsets may aggravate joint inflammation. The presence of bacterial DNA in psoriatic patient plasma has been confirmed. This increased bacterial load in the blood is due to disruption of the intestinal barrier to the access of their metabolites to the bloodstream and disruption of skin homeostasis. These findings are evidence of a relationship between the gut microbiome and skin homeostasis (Mina, 2023). While fewer Propionibacterium, Corynebacteriumi Ruminococcaceae and Akkermansia were found in psoriatic skin, more Bacteroides and Faecalibacterium were detected. Oral probiotic intake of *Bifidobacterium infantis35624* has been reported to decrease plasma levels of TNF-α when compared to control, while oral administration of *L. salivarius* LA307 and *L. rhamnosus* LA305 has been reported to decrease eczema and inflammation markers (Olejniczak-Staruch et al., 2021; Rigon et al., 2021). In a study, it was reported that the administration of *L. pentosus* GMNL-77 and *Lactobacillus sporogenes* (as a probiotic) in imiquimod-induced psoriasis animal model could suppress TNF-α, IL-6, and proinflammatory cytokines in the IL-23/IL-17 cytokines (Atabati et al., 2020; Kapoor et al., 2022).

Looking at the phylum level, patients with psoriasis had a lower relative abundance of Bacteroidetes and a higher relative abundance of Firmicutes compared to healthy controls (Chen et al., 2018; Hidalgo-Cantabrana et al., 2019; Shapiro et al., 2019). However, in a study by Huang et al., it was reported that Bacteroidetes increased and Firmicutes decreased in psoriasis (Huang et al., 2019). In addition, two other studies found reduced Proteobacteria in the psoriatic cohort (Hidalgo-Cantabrana et al., 2019; Shapiro et al., 2019). In the family level results, the relative abundance of Ruminococcaceae, Lachnospiraceae, Clostridiales Family XIII, Peptostreptococcaceae, Enterococcaceae, Coriobacteriaceae and Eggerthellaceae species increased in

psoriasis, whereas Prevotellaceae, Barnesiellaceae, Tannerellaceae, Rikenellaceae, Porphyromonadaceae, Marinifilaceae, S24-7, Lactobacillaceae, Streptococcaceae, Pasteurellaceae, Burkholderiaceae, Desulfovibrionaceae, Victivallaceae, and Verrucomicrobiaceae decreased. Conflicting results have been reported for Bacteroidaceae, Erysipelotrichaceae, Veillonellaceae, and Bifidobacteriaceae. Among these, some studies have reported that these families have decreased in psoriasis (Chen et al., 2018; Hidalgo-Cantabrana et al., 2019; Scher et al., 2015), while others have shown an increase (Hidalgo-Cantabrana et al., 2019; Tan et al., 2018). In studies at the genus level, it has been determined that Paraprevotella, Barnesiella, Alistipes, Allobaculum, Coprobacillus, Carnobacterium, Granulicatella, Rothia, Gordonibacter, Thermus were decreased in psoriasis (Codoñer et al., 2018; Hidalgo-Cantabrana et al., 2019; Huang et al., 2019; Scher et al., 2015; Tan et al., 2018). Studies have shown that the following genera are relatively increased in Psoriasis: Ruminococcus, Subdoligranum, Blautia, Coprococcus, Dorea, Christensenella, Streptococcus, Lactococcus, Enterococcus, Bacillus, Collinsella, Slackia, Bacteroides, Parabacteroides, Faecalibacterium, Lachnospira, Akkermansia, Sutterella (Codoñer et al., 2018; Hidalgo-Cantabrana et al., 2019; Huang et al., 2019; Shapiro et al., 2019; Tan et al., 2018). At the species level, *Prevotella copri, Faecalibacterium prausnitzii* and *Akkermiansia muciniphila* decreased significantly in patients with psoriasis compared to the control group; *Ruminococcus gnavus, Dorea formicigenerans, Clostridium citroniae, Escherichia coli* and *Collinsella aerofaciens* were reported to increase (Eppinga et al., 2016; Shapiro et al., 2019; Tan et al., 2018). However, these reported changes have not been confirmed in more than one study. When changes in the gut microbiota were evaluated after anti-psoriatic treatment, only one of the previous studies compared changes in the composition of the gut microbiome before and after treatment. According to Yeh et al., secukinumab treatment increased the relative abundance of the Bacteroidetes and Firmicutes phyla as well as the Proteobacteria phylum. It has been shown to cause deeper changes in the gut microbiome, such as a decrease. In addition, at other levels of taxonomic classification, secukinumab treatment caused an increase in Citrobacter at genus level and a decrease in Aeromonas, Bacteroides, Ruminococcus torques; At the family level, Enterobacteriaceae and Pseudomonadaceae increased significantly while Aeromonadaceae decreased; in contrast, no significant changes in the gut microbiome were reported after ustekinumab treatment, and only Coprococcus strains increased significantly after 6 months (Yeh, Hsu, Tsai, & Chiu, 2019).

Discussion

Considering all the above research results, it can be predicted that intestinal dysbiosis in psoriasis may be a result of different bacterial abundance rather than the number of bacterial species. In this section, several taxa with varying relative abundance in psoriasis are presented. In previous studies, a decrease in Bacteroides and Proteobacteria was reported with increasing ratios of Firmicutes and Actinobacteria at the phylum level. These four phyla make up more than 98% of the gut microbiota. Because of this, the Firmicutes/Bacteroidetes (F/B) ratio can be regarded as a key marker of the gut microbiota. Numerous studies have demonstrated a link between additional psoriatic comorbidities, like cardiovascular disorders, and an altered F/B ratio in the gut microbiome (Yoshida et al., 2018), obesity (Crovesy, Masterson, & Rosado, 2020), insulin resistance (Moreno-Indias et al., 2016), and nonalcoholic fatty liver disease (Sobhonslidsuk et al., 2018). Alteration trends of Firmicutes and Bacteroidetes are also present at lower taxonomic levels in patients with psoriasis. The severity of the illness, as well as conventional or biological therapy, can influence these modifications in the composition of the microbiome (Guerreiro et al., 2018; Zhou et al., 2020). Regarding the second important phylum Firmicutes, at least two studies have reported increased abundance of the families Ruminococcaceae and Lachnospiraceae, extinction of *Faecalibacterium prausnitzii*, and increased species level of *Ruminococcus gnavus*. *F. prausnitzii* metabolites exert a protective effect on the intestinal barrier and modulate the proinflammatory response by inhibiting NF-kB activation (Stefia et al., 2020). *F. prausnitzii* depletion has been linked to inflammatory diseases such inflammatory bowel disease and ankylosing spondylitis (Eppinga et al., 2016; Zhou et al., 2020). On the other hand, *R. gnavus* produces an inflammatory polysaccharide and contributes to intestinal barrier dysfunction. It has been found to be increased in inflammatory bowel disease, spondyloarthritis, eczema, and coronary artery disease (Toya et al., 2020). It is still unknown whether the observed imbalance between good and harmful bacteria is the cause or effect of psoriasis. In these intricate interactions between the gut microbiome and the host, tight junction proteins and gut barrier integrity are destroyed, inflammation is started and maintained, and metabolite synthesis is altered (Sikora et al., 2020; Ufnal & Pham, 2017). The control of T-cell development and function by an imbalance between Th17 and T-regulatory (Treg) cells is another theory put out to explain the relationship between intestinal dysbiosis and skin abnormalities. It has been demonstrated that alterations in the gut microbiota may encourage Th17-mediated skin inflammation in a psoriasis experimental model (Stehlikova, Kostovcikova, et

al., 2019; Zákostelská et al., 2016). The severity of psoriasis, the microbiome, and the gut barrier should all be considered in the intricate interactions in the gut-skin axis. It has been demonstrated that the blood concentration of gut barrier damage is strongly connected with the PASI. There is a significant lack of information on the possible connection between the make-up of the microbiome in the gut and the degree to which psoriasis is present. Only two of the research that were looked at investigated the possibility of a relationship between the two. According to the findings of Masallat and colleagues, there is a positive link between PASI and the ratio of firmicutes to bacteroidetes, however there is a negative correlation between PASI and the phylum Actinobacteria (Masallat & Moemen, 2016). In contrast, it was found in a study carried out by Chen et al. that the severity of the disease, as measured by the PASI score, did not have a significant impact on the abundance profile of the gut microbiota in patients who suffered from psoriasis (Chen et al., 2018). Despite the large variations in taxa that exist between the psoriasis group and the control group, this chapter made it abundantly evident that the data related microbial diversity, relative abundance, or direction of differences did not consistently reflect the same patterns. Differences in study population, design, and methodology can help explain, to some extent, the variety of the results. Psoriasis is a heterogeneous illness that can manifest itself in a diverse set of clinical manifestations. Changes in the microbiota may be caused by several factors, including disease activity, disease duration, comorbidities, and treatment, similar to those found in other chronic inflammatory diseases. In addition, in contrast to the human DNA, which is static and cannot be changed, the composition of the microbiome in the gut is very dynamic and can change depending on factors such as age, gender, regional background, and food (Knox et al., 2019; Scepanovic et al., 2019). Since the analyzed studies were not multicenter, this may explain the differences between studies. Another influencing factor may be that most studies do not examine dietary habits. Food diaries or food frequency questionnaires can be used to assess nutritional consumption for further study.

Conclusion

A greater knowledge of the intricate host-microbiome connections has been made possible by recent developments in genome sequencing and bioinformatics research. The link between psoriasis and the microbiota in the gut seems to be very complicated. Nearly all investigations on the gut microbiota's composition have noted significant alterations in psoriatic individuals. To differentiate between psoriatic and healthy people, some

metrics, such as the Firmicutes/Bacteroidetes ratio or the Psoriasis Microbiome Index, have been created (Maciel-Fiuza et al., 2023). Some authors think that "leaky gut syndrome" and bacterial translocation are a cause of the disease because they cause chronic systemic inflammation. Similar changes in the gut microbiota are seen in inflammatory bowel illnesses, obesity, and several cardiovascular diseases as well as psoriasis (Liedtke, 2023). The three most significant results in terms of changed gut physiology in psoriatic patients appear to be dysbiosis in the microbiota, a decrease in the generation of short-chain fatty acids, and dysregulation of pathways influencing the balance of lymphocyte populations (Buhaș et al., 2022). Drugs that are used to treat psoriasis can change the kinds of bacteria that live in the gut. But in some cases of biological therapy, the gut microbiota may also be able to serve as a biomarker of how well a treatment is working. However, in some instances of biological therapy, the gut microbiota may potentially function as a potential treatment response indicator.

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Chapter 10

Novel Candidate Biomarkers for Diabetes Mellitus

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ABSTRACT

Diabetes mellitus (DM) is an significant health problem because of its high mortality and morbidity rate, high treatment expenditures, and important burden to people due to the loss of the workforce. DM is a disease with high prevalence and is estimated to affect millions of people. It is a condition that comprises many complications with different causes and consequences. It can be defined as a lifelong and severe complex biochemical and metabolic disorder which described by chronic hyperglycemia resulting from a failure in insulin production, and a decrease in insulin sensitivity. Insufficient insulin secretion and/or decreased tissue against insulin response results in insufficient insulin action on different target tissues. As a result, we experience abnormalities in carbohydrate, fat, and protein metabolism. DM also plays a role in the development of secondary metabolic diseases by changing the hormone production of endocrine glands. Recent studies have highlighted novel defined biomarkers for glucose regulation and the pathogenesis of metabolic disorders such as DM. This chapter aims to present newly identified biomarkers in the diagnosis and prognosis of DM with current developments. It's proposed that determining diabetic complications earlier by using new DM biomarkers as predictors of diabetic risks and related knowledge may give valuable contributions to clinical assessments.

Keywords: Diabetes mellitus, cartonectin, afamin, fibulin, subfatin

INTRODUCTION

Diabetes mellitus (DM), as a common metabolic disease, is observed in all age groups and is characterized by hyperglycemia caused by insulin deficiency or insulin resistance. DM is a significant health problem because of high treatment expenditures and loss of workforce with a great burden to both the patient and society (Zawudie et al., 2022). The prevalence of DM, whose increasing in the world and our country, differs in population groups which depend on factors such as race, age, positive family history of diabetes, and dietary habits. Meanwhile, DM occurs as a result of absolute or relative insufficiency of insulin hormone secretion or insulin action. In addition to insulin deficiency, insulin resistance plays a significant role in the process of DM. However, it is a chronic hyperglycemic metabolic disease that causes impairments in protein, fat, and carbohydrate metabolism (Ciarambino et al., 2022).

As clinic, DM shows various symptoms such as polyuria (frequent urination), polydipsia (excessive thirst), polyphagia (excess eating), itching, and weight loss. In addition to the signs and symptoms; dry mouth, overeating or loss of appetite, blurred vision, numbness in the feet, tingling, burning, urinary tract infections, vulvovaginitis, fungal infections, dry skin, and fatigue may be observed. It also can be suspected or recognized by disease-specific side effects such as neuropathy, nephropathy, and retinopathy. There are several types of diabetes. Genetic structure, environmental factors, and lifestyle have important effects on the formation of these types. The incidence of DM is reported to be 1-2% in different populations (The Diabetic Retinopathy Study Research Group, 1978). In 2021, 11% of the global population had DM, and this ratio is expected to increase to 12% by 2045 (Hoogeveen, 2022). This increase is mainly due to the prevalence of Type 2 DM. As it continues to increase, it seems likely to become the leading cause of illness and death as worldwide.

As the pathogenesis of DM become better understood, the classification of the disease is constantly updated. The main feature is hyperglycemia in all types of DM. However, the physiopathological mechanism is differs from each other. Some types of DM involve insulin deficiency or a genetic defect that causes impaired insulin secretion. In some types, the main feature is resistance to the insülin hormone.

Symptoms and causes of DM

Based on the pathogenic mechanisms, DM is classified as Type 1 DM (T1D, insulin-dependent), Type 2 DM (T2D, non-insulin-dependent), gestational diabetes, juvenile and neonatal diabetes. Some factors play a role in

distinguishing these groups from each other. Onset situations, environmental factors, heredity, age, clinical development, and HLA gene structures are important in making this discrimination. The most important problem in T1D is β (beta) cell destruction. As a result of this destruction, insulin deficiency or absence, and abnormal insulin responses are observed in insulin receptors. It develops due to the absence or deficiency of endogenous insulin hormone secreted from the pancreas. Therefore, insulin should be included in the treatment. Autoimmune (Type 1A) cell destruction is observed in 90% of patients. Non-autoimmune (Type 1B) β cell destruction is observed in 10% of patients. Since T1D is characterized by absolute insulin deficiency, the basis of its treatment consists of eliminating this deficiency with externally administered insulin. With the invention of insulin therapy, T1D, which is among the fatal diseases, has been included in the category of chronic diseases. The incidence of T1D is generally increasing worldwide. Furthermore, the most important problem in T2D is the formation of resistance in cells against insulin activity. This resistance may be due to insulin receptors or post-insulin receptor defects. Another feature of T2D, there is generally no defect in insulin secretion and insulin structure in β cells. In this type, the decrease or absence of insulin can be attributed to the decrease of pancreatic tissues due to immune-environmental factors in the advanced stages of the disease (Zaccardi et al., 2016). Hereditary predisposition is quite high in T2D. The hereditary density of diabetes in the family occurs at earlier ages in other generations.

Although T1D occurs under the age of 30, autoimmune cell destruction may occur at any age. Whereas T2D usually occurs more frequently in older ages. It can also be observed in childhood and especially in obese people (Redondo et al., 2019). High blood glucose levels can lead to acute complications and chronic macrovascular and microvascular complications in individuals. It can cause retinopathy, nephropathy, neuropathy, cardiovascular events, diabetic foot, cerebrovascular events, and cancer formation. In addition, diabetes is the most common cause of vision loss, kidney failure, and amputation in adults (Li et al., 2023). DM is also linked with high mortality. It is reported that 6.7 million people aged 20-79 died worldwide in 2021 because of diabetes and diabetes-related causes. According to the World Health Organization (WHO), deaths due to diabetes increased by 70% from 2000 to 2019, ranking 9th among the top 10 causes of death in the world (Magliano et al., 2021).

DM has acute and chronic complications; lactic acidosis, diabetic ketoacidosis, nonketotic hyperosmolar state, and hypoglycemia are among the acute complications. Chronic complications are divided into two categories; microvascular complications including coronary artery disease, neuropathy,

retinopathy, nephropathy, and hypertension; macrovascular complications including cerebrovascular disease, and peripheral vascular disease. With the increasing prevalence of diabetes, the likelihood of complications caused by DM also increases, and this becomes a significant morbidity and mortality problem for public health. Nowadays, measurements such as fasting plasma glucose (FPG), postprandial postprandial glucose (PPG), glycosylated hemoglobin A1c (HbA1c), and oral glucose tolerance test (OGTT) are used to diagnose DM. A diagnosis of obvious DM can be made with the presence of these four criteria (Satman et al., 2017).

The American Diabetes Association (ADA) described DM as; fasting (≥ 8 hours fasting) plasma glucose (FPG) ≥ 126 mg/dL, oral glucose tolerance test (OGTT) (75 g glucose) 2nd hour plasma glucose ≥ 200 mg/dL, glycosylated hemoglobin (HbA1c) measured by the standardized method (HPLC) ≥ 6.5% (48 mmol/mol), random plasma glucose ≥ 200 mg/dL in the presence of diabetes symptoms (ADA, 2014).

The most emphasized hypothesis in the pathophysiology of DM is the metabolic hypothesis, which is related to the polyol pathway. The increased glucose is directed to alternative pathways and converted to sorbitol by the enzyme aldose reductase. Excessive activation of this pathway causes more than normal sorbitol accumulation in the cell. With excessive sorbitol accumulation, intracellular myoinositol, and taurine decrease, which leads to disruption of cell metabolism, reducing sodium/potassium-adenosine triphosphatase (Na/K-ATPase) activity and increasing intracellular oxidative stress (by reducing the amount of NADPH in the cell). This causes the nerve conduction velocity to decrease, resulting in neuropathy symptoms and signs (Brownlee, 2005). According to the recent studies, free oxygen radicals, endothelial function, and systemic inflammation biomarkers are increased at a pathological level in diabetic patients (Pitocco et al., 2013).

Considering the necessity of the current situation, fast diagnosis and the development of an effective and safe treatment option are required, so the identification of new biomarkers to predict individuals at high risk of diabetes and its complications has become a priority in targeting preventive treatment. There is a necessity to identify more specific biomarkers for a subgroup of individuals with different underlying pathogenesis and variations in the rate of disease progression that will help facilitate the prediction, prevention, and treatment of DM.

Combining biomarkers in the clinical setting may provide better sensitivity and specificity in predicting and preventing disease. Identifying novel biomarkers for DM to develop painless, non-invasive, highly sensitive

screening techniques is essential (Ortiz-Martínez et al., 2022). With further validation, these novel biomarkers can be used with or even replace conventional markers of DM. The study aims to describe novel biomarkers in types of DM and their current potential to assess risk to better clinical outcomes.

Cartonectin (CTRP-3)

Cartonectin also known as karducin, CORS-26 (collagenous repeat-containing sequence of 26-kDa protein), and C1q/TNF-related protein-3 (CTRP-3) is a new recently identified adipokine secreted from human adipose tissue that belongs to the C1q/TNF superfamily. It is secreted from subcutaneous and visceral adipose tissue and has a role in immune regulation and energy metabolism. Experimental studies confirm that CTRP3 is a secreted protein that circulates in the blood, which reflects that the physiological function of CTRP3 occurs via endocrine mechanisms. Furthermore, CTRP3 has many effects on metabolism, inflammation, proliferation, apoptosis, vascular calcification, fibrosis, and ischemic damage (Guo et al., 2020). A study declared that cartonectin has an anti-inflammatory effect by preventing inflammation induced by adipocytes, and play a role in metabolism and inflammation due to its functions similar to adiponectin (Ban et al., 2014). As an anti-inflammatory adipokine, it inhibits nuclear factor-κB signaling pathways and vehicle-like receptors and reduces TNF-α and IL-6 secretion. In addition, CTRP-3 has proangiogenic, glucose-lowering, cardio-protective, and antiapoptotic properties, and encourages adiponectin secretion (Yi et al., 2012).

In a study, it has been indicated that CTRP-3 levels are decreased in obese and hypertensive patients, and showed a negative correlation with insulin resistance, glucose, and CRP; and a positive correlation with insulin, HOMA-IR, and leptin levels. The study also suggests that CTRP-3 can be used in the early diagnosis of T2D (Ban et al., 2014). In another study, serum CTRP-3 levels were also decreased in individuals with T2D when compared to the control group. Similarly, it is stated that CTRP-3 levels are decreased in the serum of gestational diabetes (GDM) patients, and assumed that CTRP-3 has a role in the pathogenesis of GDM (Yakar et al., 2020).

A recent study reported that serum CTRP-3 levels are lower in diabetic and non-diabetic retinopathy patients compared to the non-diabetic healthy controls. They also concluded that serum cartonectin may be insufficient to distinguish both groups (Pehlivan et al., 2023). Overexpression of CTRP3 has been displayed to reduce oxidative stress and improve cell viability, and cell apoptosis in high glucose-induced retinal cells. Previous and current data

suggest that CTRP3 may be a new biomarker for diabetic retinopathy and a new tool for the treatment of diabetic retinopathy (Zhang and He, 2019).

Soha et al. determined that serum CTRP-3 concentration was significantly higher in adolescent T1D patients. In the cross-sectional study, CTRP-3 had a significant negative correlation with waist/hip ratio, total cholesterol/HDL, and triglyceride/HDL and negative correlation with HDL. They also proposed that CTRP-3 may act as a biomarker of dyslipidemia in T1D (Soha et al., 2018). Studies have revealed perturbation in the circulating levels of several adipokines in DM. As a paralogue of adiponectin, CTRP-3 has a favorable effect on insulin sensitivity and lipid metabolism. Moradi et al. Also demonstrated that serum CTRP-3 levels were significantly lower in patients with T2D and diabetic nephropathy compared to the healthy controls (Moradi et al., 2019).

Afamin

Afamin is a glycoprotein with a molecular weight of 87 kDa (15% carbohydrate content) with 55% amino acid sequence similarity to albumin, but different from albumin, it is glycosylated in a rather complex way. As previously identified as the fourth member of the albumin gene family, afamin is expressed primarily in the liver and secreted into circulating blood. In humans, the afamin gene maps to chromosome 4q11-q13. The physiological function of afamin is unknown, and it is thought to be possibly involved in transport functions for small and hydrophobic molecules (Dieplinger, 2015). A study demonstrated that afamin has a specific binding affinity in vitro for both α-tocopherol and γ-tocopherol which are two of the most important forms of vitamin E (Voegele et al., 2002).

Afamin has been shown to transport vitamin E across the blood-brain barrier with appropriate in vitro cell culture model systems, thus thought to function as an antioxidant against oxidative stress on neurons (Kratzer et al., 2009). Recently, afamin has also been shown to bind and dissolve hydrophobic, water-insoluble WNT proteins, thus preserving the ability of these proteins to activate their receptors. The WNT signaling pathway has a critical importance in stem cell development, tissue regeneration, and homeostasis. It has been shown that this signaling pathway shows an significant role in many cellular processes such as cell proliferation, survival, regeneration, and differentiation (Mihara et al., 2016). Decreased plasma afamin levels have been measured in patients with pneumonia or sepsis. In this context, it is noteworthy that it shows a very strong inverse relationship with various inflammatory biomarkers such as interleukin-6

and C-reactive protein (CRP). These results encourage new insights into afamin as a negative acute phase protein (Dieplinger et al., 2013).

A meta-analysis study (~ 20,000 individuals) shows that afamin is strongly associated with prevalence, insulin resistance, and incidence of T2D, independent of major metabolic risk factors or parameters. It is also declared that afamin may be a promising new marker in identifying individuals at high risk for the development of T2D (Kollerits et al., 2017). A recent study determined elevated plasma afamin levels in pregnant women with gestational diabetes mellitus in the first trimester but showed opposite results in the second and third trimesters. The study recommends the inclusion of afamin as a routine diagnostic test for women with gestational diabetes mellitus (Yuan et al., 2023). T1D in children is a condition in which the body no longer produces insulin. Polkowska et al. investigated serum neudesin, afamin, adropin, and in children with T1D (138 children aged between 5-18 years). According to the study, levels of serum adropin and afamin across all subgroups were lower than the control group, while neudesin levels were higher in children with T1D patients (Polkowska et al., 2019).

Body fluids such as blood and urine contain many peptides and proteins which may reflect health conditions. Advances in mass spectrometry (MS) technology can make it possible to simultaneously identify thousands of proteins and peptides in body fluids. Kaburagi et al. reported that urinary afamin levels are associated with the progression of diabetic nephropathy (DN) (Kaburagi et al., 2019). Diabetic retinopathy (DR) occurs in approximately 25% of patients with T1D or T2D diabetes. High glucose levels weaken the retinal capillaries, causing blood to leak into surrounding areas. In the following period, DR can lead to poor vision and blindness. A proteomic study concluded that the negative relationship between decreased plasma concentration levels of afamin in patients with DR and its ability to remove reactive oxygen species (ROS) from the body (because of the circulatory system's reduced ability to transport vitamin E) may be important in the pathogenesis (Lu et al., 2013).

Fibulin

Fibulin proteins are a seven-member family of secretory glycoproteins associated with basement elastic fibers, membranes, and other extracellular matrix (ECM) proteins. Proteins belonging to the fibulin family contain epidermal growth factor (EGF)-like units and a C-terminal structure. Fibulins are divided into two subgroups. The first group consists of fibulin-1 (100 kDa) and fibulin-2 (200 kDa). Fibulin-2 has two different amino-terminal regions, one rich in cysteine residues and one lacking cysteine amino acid residues. The

second group includes fibulin-3, 4, 5, 6 and 7 forms. The first three of these are defined as "short fibulins" because they have a molecular weight between 50-60 kDa. Fibulin-6 is the largest member of the family with a molecular weight of 615 kDa. Besides, fibulin-7 is newly identified and weighs about 50 kDa (Mahajan et al., 2021).

Fibulins interact with other ECM proteins, act as intermolecular bridges, bind to various supramolecular structures, and take part in cellular signaling events (Serra et al., 2015). Because of their role in the assembly and stabilization of extracellular matrix (ECM) complexes; fibulins play a role in organogenesis, vasculogenesis, fibrogenesis, and tumor formation. They are associated with ECM structures such as basement membranes, blood clots, and connective tissue fibers. In the ECM, fibulins can associate with other proteins such as fibronectin, laminin, and nidogen (Argraves et al., 2003).

Fibulin-1 is an extracellular matrix protein observed in the matrix surrounding vascular smooth muscle cells and the elastic lamina of arteries. As the most abundant in blood among other fibulins, it can be detected in serum at 30-50 μg/ml. Although its structural role is still not fully known, it has been reported that it may play a role in cell adhesion, migration, and proliferation by interacting with other ECM elements (Scarinci et al., 2019). Cangemi et al. proposed that fibulin-1 may be a factor in predicting endothelial damage in diabetic patients and mortality in cardiovascular diseases. They also concluded that fibulin-1 accumulates in the arterial wall and in plasma of patients with T2D, and appears to be a factor associated with arterial extracellular matrix changes in T2D. According to the study, patients with T2D displayed increased plasma concentrations of fibulin-1, and a positive correlation with HbA1c (Cangemi et al., 2011). In another study, it was shown that increased plasma fibulin-1 was associated with diabetes and impaired kidney function (Scholze et al., 2013).

Fibulin-1 is closely correlated with angiogenesis. A study investigated serum and vitreous fibulin-1 concentrations in diabetic retinopathy (DR) and determined that serum and vitreous fibulin-1 concentrations are elevated under DR condition (Tian et al., 2016). The pathophysiological mechanisms of diabetic nephropathy (DN) are multifactorial and complex. The typical feature of DN is the mesenchymal transition (EMT) of excessive extracellular matrix (ECM) proteins and epithelial accumulation in the tubulointerstitium, which also leads to renal fibrosis in the advanced stage. A cross-disciplinary study reported that autocrine exosomal fibulin-1 as a target of MiR-1269b induces epithelial-mesenchymal transition in the proximal tubule in DN (Tsai et al., 2021).

Subfatin

In 2004, Nishino et al. identified a protein that regulates glial cell differentiation and axonal network formation namely as meteorin (metrn). Recent studies identified metrnl as a new adipokine. Metrnl was named meteorin-like (metrnl) due to the similarity in its sequences. Meteorine is found in large amounts in the brain. However, meteorine-like (metrnl) is present in large amounts in subcutaneous adipose tissue. Therefore, the use of the term "subfatin" has been proposed (Li et al., 2023). The human subfatin gene is located on chromosome 17q25.3 and contains 311 amino acids with a molecular weight of approximately 30 kDa. Subfatin can be produced by different tissues such as the muscle, brain, spleen, heart, liver, skin, and activated macrophages (Zheng et al., 2016).

Subfatin has some effects on the human body such as inflammation inhibition, insulin sensitivity, browning of white adipose tissue, skeletal muscle regeneration, and cardioprotection. It may trigger and activate different intracellular signaling pathways in macrophages, adipocytes, cardiomyocytes, and myocytes. It is thought that subfatin plays a role in the occurrence of metabolic syndrome becuse of its effects on cardiometabolic diseases such as obesity, T2D, and coronary heart disease. Therefore, subfatin has a potential to be a therapeutic target for metabolic syndrome (Alizadeh, 2022). Peroxisome proliferator-activated receptors (PPARs), including PPAR-δ, controls the expression of numerous genes related to adipogenesis, glucose and energy metabolism, inflammation, and metabolic homeostasis. PPARs regulate multiple metabolic pathways which involved in the pathogenesis of metabolic syndrome such as T2D, nonalcoholic fatty liver disease, and cardiovascular disease (Han et al., 2017). Subfatin controls insulin sensitivity with local autocrine/paracrine activity through the PPARγ (peroxisome proliferator activated receptor-γ) pathway (Li ZY et al., 2015). In an experimental animal study, subfatin has been shown to ameliorate lipid-induced inflammation and insulin resistance via AMPK or PPARδ-dependent signaling in the skeletal muscle of mice (Jung et al., 2018).

Gestational DM (GDM) is a disease in which glucose tolerance is impaired as in T2D. Yavuzkir et al. investigated maternal and umbilical cord blood subfatin and spexin levels in patients with GDM. In the study, subfatin and spexin were significantly elevated in blood samples drawn at baseline in mothers with GDM. At the end of pregnancy, similar observations were observed in maternal and cord blood samples (Yavuzkir et al., 2020). Data on subfatin levels in patients with diabetes appear to be controversial. While a study reported that subfatin levels were lower in T2D patients (Lee et al., 2018),

another study reported that subfatin levels were higher in patients with diabetes (Chunget al. 2018). However, a recent study declared that serum subfatin levels were lower in the T2DM and prediabetes groups when compared without diabetes (Fadaei et al., 2020).

A recent study examined the plasma and aqueous levels of subfatin, preptin, and betatrophin in patients with diabetic retinopathy (DR). Plasma and aqueous subfatin levels were higher in DR compared to controls (Güngör et al., 2023). Hybrid diabetes or double diabetes (DD) occurs when the patients exhibit characteristics that combine T1D and T2D. A significant increase in the serum levels of subfatin in DD patients was determined and supposed that subfatin level could be used as a novel biomarker of DD and may contribute to the early diagnosis of diabetes (Hassan et al., 2023).

Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes. It accounts for 25-35% of T2D and significantly increases the mortality of patients with T2D. Serum subfatin concentrations were significantly decreased in T2D patients with the macroalbuminuria group than in the other T2D subgroups. Also, the study showed a correlation between serum subfatin and a decreased risk of T2D and DN (Wang et al., 2020).

CONCLUSION

Although significant progress has been made with the investigations, more research is needed for new biomarkers for DM. Developments in this field are very important in reducing the incidence of DM and improving the prognosis of the disease. Research on novel biomarkers may give valuable contributions to the diagnosis and management of DM. Nowadays, investigations on the relationship between mentioned biomarkers and diabetes are ongoing. In sum, it seems that further and comprehensive studies are needed to clarify the full potential of cartonectin, afamin, fibulin, and subfatin for DM disease.

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Chapter 11

Stoma and Care Bundles

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INTRODUCTION

Care bundles can be defined as the application of several evidence-based practices to a certain patient group and care setting, which results in better results than the application of evidence-based practices alone. Care bundles are important in standardizing the care given to patients. The ventilator care bundle and central catheter care bundle were among the first to be developed. However, the development and use of care bundles are increasing in many patient groups and care settings (Resar et al., 2012:2; Candas and Gürsoy, 2017:233). It is necessary to draw attention to care bundles for stomas, which directly affect the quality of life and can lead to serious complications if good care is not provided (Su et al., 2021:224).

CARE BUNDLES

Care bundles came to the fore for the first time in 2001 with the "Ideal Design of Intensive Care Units" project in cooperation with the Voluntary Hospital Association and the Institute for Healthcare Improvement. This project initiative was planned to re-examine the care provided in intensive care units and the design of intensive care units. By collaborating with the Voluntary Hospitals Association and the Institute for Healthcare Improvement and the team working in the intensive care units of 13 hospitals, it was aimed to redesign the intensive care units, improve the quality of care with the highest reliability, and increase team communication and cooperation. All these processes include the participation of the patient and family, in addition to multidisciplinary teamwork (Resar et al., 2012:2; Candas and Gürsoy, 2017:234).

Care bundles were a key part of the “100,000 Survivors Program” in 2004 and the “5 Million Survivors Campaign” in 2006, launched by the Institute for Healthcare Improvement. These programs and campaigns are designed to improve patient safety and quality of care in various medical conditions such as sepsis and heart and respiratory failure in intensive care units. During the same period, the "Living Sepsis Campaign" was promoted internationally. This campaign aims to increase the survival rate in severe sepsis patients by 25% in 2009 (Horner and Bellamy, 2012:199).

Care bundles, which are increasingly used in many patient groups and care settings, are essentially a bundle consisting of 3-5 evidence-based practices. These evidence-based practices are relatively independent of each other. The care bundle should be created suitable for a certain patient group and a certain setting. The creation and implementation of the care bundle should be achieved through multidisciplinary collaboration. Each application that makes up the

bundle is an application with evidence level I and II obtained from randomized controlled experimental studies. While each practice on its own leads to positive results in patient care, the level of well-being should increase when applied together. As a basic principle, all components must be compatible with each other. Each stage in the care bundle should be expressed clearly and understandably and should contain descriptive information rather than prescriptive information. Compliance with all practices that make up the care bundle is measured by recording "yes" when the intervention was made or "no" when the intervention was not made. When a "no" answer is given to one of these applications, the care bundle is considered incomplete. In other words, care bundles are applied with an "all or nothing" approach. The care bundle compliance rate must be over 95%. When calculating the compliance rate, the percentage value of the ratio of the number of patients to whom the care bundle is applied to the number of patients to whom the care bundle should be applied is calculated. If this rate is below 95%, it should be considered not applicable (Resar et al., 2012:5; Candas and Gürsoy, 2017:236; Horner and Bellamy, 2012:200).

The care bundles are easy to audit and develop. In addition, care bundles facilitate the reflection of research-proven practices into clinical practice. It reduces the carelessness of healthcare professionals. It increases communication both between healthcare professionals and with the patient and family. It ensures effective use of healthcare resources and reduces costs. It reduces morbidity and mortality, hospital stay and complications. Increases patient safety. Provides standardization in the care given to patients (Sayın, 2017:146; Kurutkan, 2014:87).

While developing the care bundle, some steps need to be completed. First, an issue and problem for which a care bundle should be developed should be determined in cooperation with the multidisciplinary team. All initiatives and practices should be listed in line with the determined topic. A comprehensive literature review is conducted regarding these initiatives and practices. In the literature review, randomized controlled experimental studies, meta-analysis and systematic reviews containing these studies, clinical practice guidelines and expert opinions are obtained. When conducting a literature review, it is important to use peer-reviewed journals and databases that will provide accurate information on the subject. Cumulative Index to Nursing & Allied Health (CINAHL) and the US National Library of Medicine (PubMed) are among the sources that can be used to access peer-reviewed journals. In addition, the Cochrane Library is a database that can be used to access research evidence that can be applied to larger samples. The US resource The National Guideline

Clearinghouse is among the resources that bring together current evidence-based practices. However, each country's own database should also be examined. The research obtained as a result of the literature review is examined. These studies are classified according to the level of evidence. Studies that do not have evidence levels I and II should be excluded from the intervention and practice list. Depending on the patient group and setting where the care bundle is planned to be applied, the practices that will form the care bundle should be decided in cooperation with the multidisciplinary team (Sayın, 2017:149; McCarron, 2011:33; Taksande et al., 2020:258).

STOMA AND CARE

A stoma is an opening created by surgically inserting an organ into the skin. The most commonly created stomas include colostomy, ileostomy and urostomy (Salom et al., 2019:285; Ambe et al., 2018:182). Stomas are most commonly created due to cancer. According to the data of the International Agency for Research on Cancer in 2020, colorectal cancer ranks 3rd and bladder cancer ranks 10th in all ages and genders (International Agency for Research on Cancer, 2020). It is estimated that 18-35% of patients diagnosed with colorectal and bladder cancer undergo temporary or permanent stoma surgery (Mo et al., 2021:462).

Although stomas are lifesaving, they lead to radical changes in the lives of individuals (Capilla-Díaz et al., 2016:39). Stomas cause many difficulties regardless of whether they are temporary or permanent (Cross, 2023:34; Wound, Ostomy and Continence Nurses Society and Guideline Development Task Force, 2018:50). Additionally, when examined in terms of complications, it is estimated that individuals with stoma experience complications at a rate of 10-70% (Ambe et al., 2018:184). Individuals need to receive multidisciplinary care from healthcare professionals, especially nurses, in order to adapt to this new life and body image, prevent complications and maintain stoma care. This care should cover a wide period of time, from pre-operative to post-operative discharge. Nurses play a key role in ensuring multidisciplinary collaboration and coordinating the family's participation in the individual's care (Cross, 2023:34).

When the literature on stoma care is examined, it is seen that there are many evidence-based studies and guidelines. In this regard, evidence-based practices include preoperative, intraoperative, postoperative and discharge processes (Wound, Ostomy and Continence Nurses Society and Guideline Development Task Force, 2018:51; Hendren et al., 2015: 375; Chabal et al., 2021: 294; Roveron et al., 2021: 137; 19. Registered Nurses' Association of Ontario,

2019:9; Ferrara et al., 2019: 1038; Miller et al., 2017: 74; 15-22; Li et al., 2022:1517).

In the preoperative period, patients and their families should be educated using various methods such as verbal, written, and digital applications. The content of the education should include topics such as the basic anatomy and physiology of the system in which a stoma is planned to be opened, surgical method, type and location of the stoma, stoma care products, and stoma care. Providing preoperative education to patients and their families provides psychological preparation. In addition, with training, stoma management becomes easier for patients after surgery, their quality of life increases and the average length of stay in the hospital decreases. (Level of Evidence: IB) A specialist nurse, such as a stoma care nurse, should be included in preoperative education. (Level of Evidence: IB) The area where a stoma will be created should be determined before surgery with the participation of the stoma care nurse, surgeon and patient. Determining the area where a stoma will be created makes it easier for patients to continue their daily life activities and self-care while reducing complications. (Level of Evidence: IB) (Wound, Ostomy and Continence Nurses Society and Guideline Development Task Force, 2018:53; Hendren et al., 2015: 381; Chabal et al., 2021: 296; Roveron et al., 2021: 138; Registered Nurses' Association of Ontario, 2019:13; Ferrara et al., 2019: 1039; Miller et al., 2017: 75; Li et al., 2022:1526).

If possible, laparoscopic surgery should be preferred over open surgery when creating a stoma during surgery. (Level of Evidence: IC) Having stomas at least 1 cm above the skin level reduces complications. (Level of Evidence: IC) (Hendren et al., 2015: 376; Registered Nurses' Association of Ontario, 2019:47; Ferrara et al., 2019: 1041; Li et al., 2022:1526)

In the postoperative period, the stoma and peristomal area should be evaluated with a validated tool in terms of complications, and the evaluation should be repeated at each stoma care. (Level of Evidence: IA) The information given to patients and their families during the preoperative phase should be reinforced after the surgery. (Level of Evidence: IC) The patient and family should be encouraged to participate in stoma care and management. (Level of Evidence: IB) Care should be provided by a stoma care nurse to help the patient choose the appropriate bag and adapter system. (Level of Evidence: IC) When deciding on this bag and adapter, the individual's characteristics such as stoma type and location, abdominal condition, lifestyle, personal preferences, vision, and dexterity should be taken into consideration. (Level of Evidence: IC) Before applying the bag and adapter, the size of the stoma should be measured and the size of the adapter should be adjusted according to the size. (Level of

Evidence: IC) Patients should be evaluated for risk factors for stoma and peristomal area complications. The patient and family should be educated about recognizing complications. (Level of Evidence: IA) It is important for patients to acquire and learn stoma care skills before discharge. Patients should be able to ensure that the stoma and peristomal area are evaluated, stoma care, emptying and changing of the stoma bag, and provision of stoma materials before discharge. Additionally, education on topics such as gas and odor management, recognizing complications, nutrition, and fluid intake should be repeated. (Level of Evidence: IB) Colostomy irrigation can be applied to stomas in the sigmoid and descending colon. (Level of Evidence: IIC) (Wound, Ostomy and Continence Nurses Society and Guideline Development Task Force, 2018:54; Chabal et al., 2021: 296; Roveron et al., 2021: 144; Registered Nurses' Association of Ontario, 2019:13: Ferrara et al., 2019: 1048; Miller et al., 2017: 76; Li et al., 2022:1526).

After discharge, follow-up care and support should be provided through an outpatient stoma clinic, home health services, and telephone. (Level of Evidence: IIC) Individuals with stoma should be followed up for 12 months after surgery so that they can effectively manage and cope with the process. (Level of Evidence: IC) Patients should have a follow-up phone call with the stoma care nurse within 7-10 days of hospital discharge to assess their compliance with the stoma. (Level of Evidence: IC) Follow-up intervals of 2, 4 and 6 weeks with the stoma care nurse are recommended. Follow-up frequencies should be determined according to the needs of the patient and family. (Level of Evidence: IA) Information about community-based stoma support groups and online stoma support groups should be provided to facilitate stoma adaptation. (Level of Evidence: IC) (Wound, Ostomy and Continence Nurses Society and Guideline Development Task Force, 2018:54; Hendren et al., 2015: 383; Roveron et al., 2021: 139; Registered Nurses' Association of Ontario, 2019:14: Miller et al., 2017: 76; Li et al., 2022:1526).

THE PLACE OF CARE BUNDLES IN STOMA CARE

Although there are many evidence-based studies on stoma care, the literature on stoma care bundles is limited.

Su et al. (2021) conducted a randomized controlled trial on the health outcomes of an evidence-based care bundle in rectal cancer patients with temporary stomas. The control group received routine care. Routine care includes determining the stoma site before surgery, involving the stoma care nurse in providing patients with stoma care and guiding them to prevent complications, and visits with volunteers from stoma support groups to share

their stoma self-care experiences, advice on medication use, nutrition, and social activities. After discharge, outpatient follow-ups and, when necessary, telephone conversations with nurses initiated by the patient are carried out without a specific time. The stoma self-management guide, outpatient follow-ups, and telephone interviews were collectively administered to the experimental group. The self-management guide consisted of individual stoma records, individual stoma self-management, daily self-management, individual self-management chart, and contact information of the medical team. Patients were informed by the stoma care nurse about the stoma self-management guide and basic information about the stoma within 24 hours after being admitted to the hospital for stoma surgery. After surgery, patients' knowledge and practices regarding stoma self-management skills were recorded in the individual self-management chart in the stoma self-management guide. During outpatient follow-up, a control appointment was made at the stoma polyclinics in the 4th week after the surgery. This check was performed by the stoma care nurse and took at least 20 minutes. Patients were evaluated for stoma care and stoma-related complications. Additionally, the patient's stoma self-management plan was reviewed. Information is recorded in the individual self-management chart. After discharge, phone calls were made by the stoma care nurse on days 3 to 7, 14 to 20, 27 to 30, and 87 to 90, each lasting 10-20 minutes. During the telephone calls, patients were asked questions about their stoma experience, feelings, stoma-related signs and symptoms, stoma care ability, and self-confidence. When necessary, patients were given advice by the stoma care nurse. At the end of the phone calls, an appointment was made for the next phone follow-up. As a result of this study, stoma self-efficacy, quality of life, and care satisfaction of the experimental group were found to be significantly higher than the control group. In addition, the time taken for stoma closure and the incidence of complications were found to be significantly lower in the experimental group than in the control group. As a result of this study, it was concluded that the care bundle applied to continue post-discharge care was effective in improving the health outcomes of individuals with stoma (Su et al., 2021:223).

Pan et al. (2022) conducted a randomized controlled study examining the effect of post-discharge continuing care bundle in patients with permanent stoma. The control group received traditional care, including discharge education, regular follow-up visits in the hospital, and telephone follow-up. The continuing care bundle group was provided care by the care bundle team consisting of health professionals such as doctors and nurses. After discharge, telephone follow-ups were made once a week, with each call lasting 10-20

minutes. These telephone follow-ups continued for 3 months. During phone calls, patients' questions were mainly focused on and their questions were answered. As a part of the continuing care bundle, home care nurses and family members met twice a week on an online platform in order to understand the patient's condition and eliminate deficiencies in care. Home visits were made twice a month for 30 minutes to observe stoma-related problems and the patient's physical recovery status, provide additional education on stoma management, and provide care materials such as stoma bags. In addition, patients were followed up at the outpatient clinic to diagnose and treat complications through stoma self-management care. Patients' stoma self-efficacy, self-care knowledge, ability to change the stoma adapter, negative emotions, quality of life, and patient satisfaction were observed 1 and 3 months after discharge. As a result of the study, self-efficacy, self-care knowledge, ability to change the stoma adapter, quality of life, and satisfaction were found to be significantly higher in the care bundle group compared to the control group. Additionally, there was a decrease in depression and anxiety in the care bundle group (Pan et al., 2022:1).

CONCLUSION

Care bundles have been used in healthcare for approximately 20 years. Care bundles provide the use of 3-5 evidence-based practices, which are considered good practices, in patient care. Today, care bundles have been developed for many patient groups and care settings. On the other hand, it appears that there are evidence-based guidelines for stoma care in the literature, but care bundles are limited. It is thought that the use of care bundles in stoma care will increase patients' self-care and reduce their complications.

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