JUNE, 2025

Academic Research in Health Sciences

Editors
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DOI: 10.5281/zenodo.15762498

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Publisher
Platanus Publishing®

Editor in Chief
Prof. Salim Güngör, Ph.D & Assoc. Prof. Bülent Işık, Ph.D.

Cover & Interior Design
Platanus Publishing®

The First Edition
June, 2025

ISBN

979-828-9993-05-2

Platanus Publishing®
Address: Natoyolu Cad. Fahri Korutürk Mah. 157/B, 06480, Mamak, Ankara, Turkey.

Phone: +90 312 390 1 118
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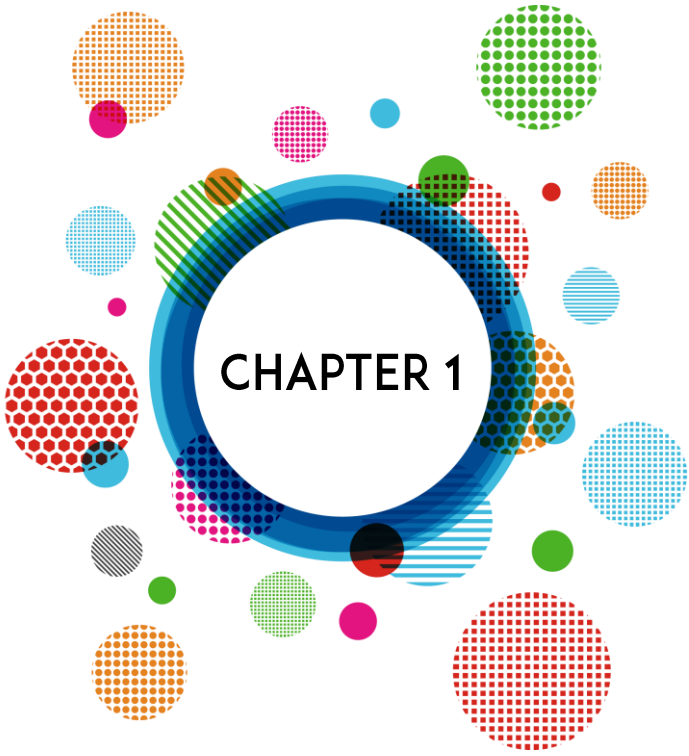

Osteoporosis and Bıomechanical Properties of Bone

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INTRODUCTION

Osteoporosis is the most common metabolic bone disease characterized by a marked decrease in bone mass and deterioration in the microarchitecture of bone tissue, which increases the risk of fractures (Johnell and Kanis, 2006; Eastell et al., 2016).

This disease is diagnosed using the T-score determined by bone densitometry performed on the proximal femur and spine. A T-score below 2.5 standard deviations from the mean of the reference young population may indicate the presence of osteoporosis (Wright et al., 2014).

Osteoporosis is a health problem of worldwide importance, causing nearly 9 million fractures worldwide every year (Johnell and Kanis, 2006; Hareket and Gürşan, 2023). As the population ages, the costs and problems associated with osteoporosis are increasing. It is estimated that the annual medical cost of the disease in the USA is 19 billion dollars and the total cost of a single patient for a hip fracture can reach 45 thousand dollars (Hareket and Gürşan, 2023). In a study conducted in Turkey, it is estimated that 1.35 million fractures will occur between 2019 and 2023 due to osteoporosis, leading to a cost of 2.42 billion dollars (Aziziyeh et al., 2020).

Osteoporosis is a major health condition that affects the lives of approximately one in two women. Because women generally have lower bone density and mineral content than men, they tend to lose bone at a younger age and at a faster rate. Accordingly, it emphasizes that osteoporosis is four times more common in women aged 50 years and older than in men, and the risk of early fracture is 5-10 years higher (Hareket & Gürşan, 2023; Aziziyeh et al., 2020).

Bones are organs consisting of bone tissue, bone marrow and connective tissue called periosteum surrounding these structures, with a dense vascular and nerve network. Bones, which are the basic component of the skeletal system, provide protective and production space for the bone marrow where the hematopoiesis process takes place, in addition to their functions of protecting, supporting and providing movement (Barrere et al., 2006).

Bone undergoes longitudinal and radial growth, remodeling and remodeling throughout life. These processes allow bone to adapt to biomechanical forces and fulfill bodily functions (Dohrn et al., 2016).

Biomechanics is a branch of science that studies the effects of internal or external forces on living systems using engineering methods. Bone biomechanics, an important sub-branch of this discipline, specifically evaluates the fragility and strength properties of bone. The mechanical strength and fracture tendency of bone are the result of a complex interaction of bone mass or density, architecture/geometry and material properties of the bone matrix (Kutsal, 2004). To describe the brittleness

of bone from a biomechanical point of view, three key components are usually taken into account; endurance or strength, frangibility or deformability, and the amount of energy the bone can withstand before fracture. These parameters are measured by biomechanical tests including compression, tensile and shear forces performed in the laboratory (Turner, 2002).

Definition of Osteoporosis and its Effects on Bone Health

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mineral density and deterioration in bone microarchitecture (Kutsal, 2004). These pathologic changes significantly reduce the mechanical strength of bones, leading to an increased risk of fracture even in minimal trauma. In the osteoporotic process, the compact and spongy structures of bone are disrupted, which negatively affects both the microstructural integrity and mechanical strength of bones.

Osteoporotic bones exhibit lower toughness and increased brittleness compared to normal bones. Toughness refers to the amount of energy a bone can absorb before fracture, while brittleness refers to the ease of fracture with low deformation capacities (Turner & Burr, 1993). The fragility level of bone tissue is directly related to structural factors such as the geometric shape, diameter, textural density and microarchitectural features of the bone. In this context, it should be emphasized that osteoporosis is defined not only by a decrease in bone mass but also by deterioration in the structural quality of bone.

Biomechanical Properties of Bone

The biomechanical properties of bone are the basic parameters that determine the functional competence of the skeletal system. These properties are defined by criteria such as deformation of the bone against the applied force, stiffness, elastic modulus, energy absorption capacity and resistance to fracture (Turner & Burr, 1993; Martin, Burr & Sharkey, 2004).

1.1 Force and Deformation

Force is a physical vector quantity with direction and magnitude and is expressed in units of Newton (N) (An, Barfield & Draughn, 2000). The force applied externally to the bone causes changes in structural integrity. This change in the bone as a result of force application is called deformation. Deformation can be observed as elongation, shortening or angular deformation of the bone (Delehay & Wiesel, 2001). The elastic deformation capacity of bone refers to its ability to return to its original shape when the load is removed, while plastic deformation describes the permanent shape changes of bone. In healthy bones, elastic deformation is predominant; in osteoporotic bones, the rate of plastic deformation increases.

1.2 Stress and Strain

Stress refers to the amount of applied force per unit area and is measured in N/mm² or MPa. Stress indicates how the bone distributes the load at the tissue level (Chao et al., 2012). Strain is the relative rate of change in the dimensions of the bone as a result of the applied force and is defined as a unitless rate.

Stress-strain curves are critical in understanding the behavior of bone tissue between elastic and plastic regions (Martin et al., 2004). In the elastic region of the curve, bone can return to its original form when the load is removed, whereas permanent deformations occur in the plastic region. In osteoporotic bones, the elastic limit values decrease and plastic deformation starts earlier.

1.3 Rigidity and Elastic Modulus

Stiffness represents the slope in the elastic region of the force-deformation curve and is a measure of the resistance of bone to deformation (An & Friedman, 1999). Bones with high stiffness deform less under load. The elastic modulus is determined by the slope of the elastic region of the stress-strain curve and reflects the stiffness of the bone (Turner & Burr, 1993; Delahay & Wiesel, 2001). Elastic modulus is an important indicator of the load carrying capacity of bone. In osteoporotic bones, a decrease in elastic modulus values occurs, which contributes to a decrease in mechanical strength (Sevil & Kara, 2013).

1.4 Toughness and Fragility

Toughness is the total energy absorption capacity of bone against fracture. Bones with high toughness can remain unbroken even under high energy loads (Turner & Burr, 1993). In osteoporotic bones, this capacity is severely reduced. Brittleness refers to the ease with which bone can fracture when its deformation capacity is low. In osteoporosis, brittleness increases, this leads to an increased risk of spontaneous fracture (Sevil, 2006).

2. Biomechanical Changes in Osteoporosis

Osteoporosis causes significant changes in bone structure at both macroscopic and microscopic levels. Studies have shown that in osteoporotic bones, ultimate strength is significantly decreased, deformation capacity is increased and energy absorption is severely reduced (Sevil & Kara, 2010).

Especially in experimental studies, it was reported that the energy absorption capacity of osteoporotic rabbit femurs decreased significantly, the load-bearing capacity of the bone decreased and fracture formation became easier (Sevil, 2006). These results show that osteoporosis causes dramatic changes not only in mineral

loss but also in the mechanical and viscoelastic properties of bone. Furthermore, micromorphologic changes in osteoporosis, such as thinning of cortical bone thickness and dilution of trabecular bone structure, further increase the loss of mechanical strength.

3. Biomechanical Testing of Bone and Evaluation of Osteoporosis

Various mechanical tests are used to evaluate the biomechanical performance of bone. These tests include compression, tension, bending and torsion tests (An et al., 2000; Shahar, Banks-Sills & Eliasy, 2003). Each test offers unique advantages in analyzing different mechanical properties of bone.

Compression Tests: Measures the strength of bones against loads applied in the axial direction. It is especially used in the evaluation of bones exposed to compression such as vertebrae.

Tensile Tests: Determines the strength and elastic limits of bones against tensile forces.

Bending Tests (Three Point Flexure Test): It allows to analyze both elastic and plastic deformation capacity of the bone. It is often preferred in osteoporosis studies (Frankel & Nordin, 2001).

With these tests, critical parameters such as the elastic limit point, ultimate strength and deformation capacity of the bone can be measured. These measurements allow quantitative assessment of the biomechanical effects of osteoporosis. These methods are also used to monitor the effectiveness of pharmacologic treatments and other osteoporosis prevention strategies.

4. Definition of Osteoporosis

Osteoporosis is a disease with different definitions and evolving definitions over time. It was first called "pore bone" by Jean Georges Lobstein in 1829. Then, it was defined by Albright in 1948 as "too little bone within bone". In the 2000 Osteoporosis Conference, it was described as "a musculoskeletal disorder characterized by loss of bone strength that increases the risk of fractures". It is important to know Bone Mineral Density (BMD) values for the diagnosis of osteoporosis (Bartl et al., 2006; Kutsal, 2012).

The definition of osteoporosis was revised in 1996 at the World Congress on Osteoporosis in Amsterdam. The diagnosis is now made using Dual X-Ray Absorptiometry (DEXA), which determines the presence or absence of fractures as well as Bone Mineral Density (BMD) values. According to the definition:

Normal: BMD or bone mineral content less than 1 standard deviation below that

of a young adult,

Osteopenia (low bone mass): BMD between -1 SD and -2.5 SD compared to young adults,

Osteoporosis: BMD below -2.5 SD compared to young adults,

Acquired Osteoporosis: It is defined as BMD below -2.5 SD compared to young adults and one or more fractures (Cooper, 1989; Guyton et al., 1996; Miller et al., 2004).

The main goal in maintaining skeletal health is the implementation of primary prevention. Therefore, the diagnosis of "osteopenia" is becoming increasingly important. Especially in osteopenic postmenopausal women, measures to preserve skeletal mass are a priority. The definition of osteoporosis emphasizes microstructural changes in bone with loss of bone mass and decreased strength (Miller et al., 2004; Thomas et al., 2008; Ferguson et al., 2009).

Disruption of trabecular integrity is a prominent feature of osteoporotic bones. In this case, thinner rather than thicker trabecular plates are seen and a severe disruption of the trabecular structure occurs. Furthermore, the cement lines formed during bone remodeling mark the junction of new and old bone lamellae (Bouxsein, 2001).

Increased cortical porosity is associated with an increase in the number and size of voids in the bone cortex. This is considered an indicator of deterioration in the internal structure of bone tissue and is an important symptom of osteoporosis. Increased cortical porosity can negatively affect the strength and durability of bones, as these voids disrupt the integrity of bone tissue and increase the risk of bone fracture (Guyton et al., 1996).

On the other hand, bone fatigue is characterized by the deterioration of the elasticity of compact bone tissue as a result of continuous overloading. Normally, bones should be able to withstand the forces applied to the body; however, bones that are constantly under load may wear out and weaken over time. This is especially common in individuals with high levels of physical activity and during the aging process (Guyton et al., 1996; Miller, 2004). Bone fatigue can reduce the strength and fracture resistance of bones, which is one of the possible consequences of osteoporosis (Aloia, 1989; Raisz, 2005).

5. Incidence of Osteoporosis

Osteoporosis is recognized globally as a serious public health problem. Each year, more than 1.5 million people are diagnosed with osteoporosis. The disease causes more than 700,000 spinal fractures and more than 300,000 hip fractures per year

(Van Staa et al., 2001; Parsons, 2005). Over the next 15 years, the number of hip fractures is expected to double and quadruple by 2041. In the United States, more than 10 million people have osteoporosis and 34 million have osteopenia (reduced bone mineral density); 80% of these cases are women. In Spain, approximately one million women have osteoporosis, which means that a quarter of women aged 50 years and over are struggling with osteoporosis (Işık and Cankurtaran, 2006; Rizer, 2006). Although there are no exact records in Turkey, it is estimated that there are approximately 8 million people with osteoporosis (Parsons, 2005). Hip fractures cause the highest mortality and loss of functionality among osteoporotic fractures. After a hip fracture, 20-25% of patients die within one year and 25% require long-term care. Furthermore, the rate of those who cannot fully return to their pre-fracture lifestyle is around 50% (Işık and Cankurtaran, 2006).

6. Pathophysiology of Osteoporosis

Osteoporosis may occur without a marked decrease in bone mineral density and this may lead to fractures with minor trauma. Although most postmenopausal women have estrogen deficiency, osteoporosis and related fractures develop in only a fraction of them. The main factors involved in this condition include low peak bone mass (MBM) and changes in bone quality and microstructure (Frontera et al., 1999). DKK is defined as the highest bone mass that an individual can reach during his or her lifetime. With increasing age, bone loss increases and this is an important factor affecting fracture resistance. The process of reaching DKK usually starts at 17-18 years of age and continues until 35 years of age at the latest (Renno et al., 2005).

Bone is subject to a continuous process of building and breaking down throughout life. Osteoporosis is associated with a decrease in bone formation or an increase in bone resorption. In women, estrogen deficiency, especially with menopause, is the leading cause of bone loss. The increase in bone resorption due to estrogen deficiency leads to changes in calcium metabolism and a decrease in calcitonin release (Parfitt, 2002; Ferguson et al., 2009).

The aging process causes marked changes in bone structures. These changes include primarily a decrease in osteoblast activity and a consequent decrease in calcium absorption. Calcium deficiency can contribute to low calcium levels and consequent factors that can affect bone health. Vitamin D deficiency and the associated development of hyperparathyroidism can lead to accelerated bone turnover and consequently bone loss (Nguyen et al., 1998; Kutsal, 2012).

7. Risk Factors of Osteoporosis

Today, osteoporosis has become a major health problem. It is vital to identify risk

factors to prevent this disease. Risk factors are generally categorized into structural and genetic characteristics, lifestyle and dietary habits, medical conditions and environmental factors (Cooper, 1989).

Osteoporosis is a disease caused by the interaction of a complex set of factors. These factors usually range from structural, genetic, lifestyle and dietary habits to medical conditions and environmental factors. In terms of lifestyle and dietary habits, narrow risk factors include leading a sedentary lifestyle, insufficient calcium and vitamin D intake, excessive coffee consumption, alcohol consumption, smoking, excessive salt and protein intake. In terms of medical conditions, the use of certain medications (corticosteroids, thyroid drugs, heparin, diuretics, etc.), surgical menopause, malabsorption due to gastrointestinal problems, chronic renal failure, hyperparathyroidism can also increase the risk of osteoporosis. However, environmental factors also play a major role; slippery and wet floors, poor weather conditions, inadequate lighting, unfamiliar stairs and flooring, objects to trip over on the floor can also affect the risk of osteoporosis. The interaction of these factors has a complex effect on the development of osteoporosis and it is important to consider all these factors to understand and prevent the development of the disease. People with blond hair, blue eyes, thin skin and thin body build are at higher risk of osteoporosis, as are Caucasians. There are racial differences in bone density; blacks generally have higher bone volume and weight than whites, which may reduce the risk of fractures. Genetic factors have a great influence on bone health; women with a family history of hip fracture have an increased risk of fracture (Rizer, 2006; Cooper, 1989; Miller et al., 2004).

Menopause is one of the main causes of osteoporosis. Estrogen deficiency accelerates bone loss. Also, body weight is important for bone health; obesity can have a protective effect. Inactivity and sedentary living can reduce bone density. Smoking, alcohol and caffeine consumption negatively affect bone health (Mackie et al., 2008).

Calcium and vitamin D deficiency may increase the risk of osteoporosis. Vitamin D deficiency can negatively affect bone health and mineralization. Women have a higher risk of osteoporosis than men due to decreased estrogen levels. Hyperparathyroidism also has an impact on bone health; excess parathyroid hormone increases the release of calcium from bones. Environmental factors can also increase fracture risk and accelerate the development of osteoporosis (MY, 2000; Thomas et al., 2008).

8. Clinical Findings in Osteoporosis

Osteoporosis is a condition that often leads to fractures and causes pain,

deformity and loss of function. Osteoporosis has a long period of silence before clinical signs or complications develop and is called "asymptomatic densitometric osteoporosis". Diagnosis during this period is important (Cadarette et al., 2000; Kerschan-Schindl et al., 2001). Clinical findings include back pain, decreased neck height, spinal deformities, presence of periodontal disease and fractures. The pain usually increases with activity and is particularly pronounced during weight lifting. The pain is typically mild and persistent. Bones can be painful to the touch or with mild impact. Pain is often caused by conditions such as poor posture, ligament strain or chronic spinal fractures. In acute spinal fractures, sudden and severe pain is common and spasm of the paravertebral muscles may be seen. Fractures are usually localized in the T12 or L1 vertebrae and these fractures of the spine may shorten the neck length (Lombardi et al., 2004; Lombardi et al., 2005).

The clinical signs and symptoms of osteoporosis often occur as a direct or indirect consequence of fractures. The most common symptom in these patients is usually bone pain. Osteoporosis, with its impact on the musculoskeletal system, can cause chronic pain, decreased functional capacity and reduced quality of life. The most common types of fractures are hip, vertebral and Colles fractures (Lips et al., 2005; Vik et al., 2005). Hip Fractures: Hip fractures usually occur in the femoral neck or intertrochanteric region. They have a high morbidity and mortality rate and usually occur as a result of falls (Marcus, 1996; Thomas et al., 2008).

Vertebral Fractures Vertebral fractures can usually occur with minimal trauma or spontaneously. Symptomatic vertebral fractures can cause significant morbidity and are associated with certain vertebral deformities. These fractures, which occur in the thoracic or lumbar vertebrae, may limit patient function and ambulation (Bartl et al., 2006; Beyazova and Kutsal, 2016).

Colles fractures Colles fractures increase with age and decreased postural stability. These fractures occur when the radius fractures above the wrist joint as a result of a fall on the hand. Treatment may include reduction and plaster cast application, but some complications may occur (Bartl et al., 2006; Bayrak, 2014). The clinical manifestations of osteoporosis and the frequency of fractures increase with age and can significantly affect quality of life (Marcus, 1996).

9. Diagnostic Methods

Osteoporosis can be diagnosed by measurement of bone mass or istomorphometric studies. The diagnostic approach should include detailed history taking, physical examination, biochemical investigations, imaging modalities and bone biopsy. Routinely recommended procedures include history and physical examination, laboratory tests, conventional radiography and measurement of bone

mineral density by Dual Energy X-ray Absorpsiometry (DEXA) (Beyazova and Kutsal, 2016). The aims of diagnostic methods for osteoporosis include: excluding diseases that mimic osteoporosis, understanding the causes and contributing factors of osteoporosis, assessing the severity of the disease, determining the prognosis and subsequent fracture risk, selecting appropriate treatment and ensuring subsequent follow-up of treatment (Tekin et al., 2005). Although routine laboratory findings are usually within normal limits in patients with primary osteoporosis, marked changes may be observed in secondary osteoporosis. To exclude the possibility of secondary osteoporosis, tests such as hemoglobin, leukocyte and leukocyte formula, erythrocyte sedimentation rate, fasting blood glucose, creatinine, serum calcium, phosphorus, total alkaline phosphatase and liver function tests should be performed. With these tests, secondary causes of osteoporosis such as diabetes mellitus, chronic liver diseases, nephropathy, hematologic malignancies and cancers with bone metastases can be excluded. In addition, tests such as calcium/creatinine ratio, serum and/or urine electrophoresis, thyroid stimulating hormone (TSH), parathormone, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, plasma testosterone or estradiol levels, and serum cortisol levels can be used to rule out other diseases (Bayrak, 2014).

10. Biochemical diagnostic methods

Biochemical diagnostic methods in osteoporosis are mainly based on the study of parameters related to the products of formation and resorption in the bone cycle. Biochemical indicators of bone formation include alkaline phosphatase, osteocalcin and propeptides of type 1 collagen. Isoenzymes of alkaline phosphatase are found in various tissues such as bone, liver, intestine, kidney and placenta. In healthy individuals, approximately 50% of this enzyme is of bone origin. Serum total alkaline phosphatase activity is the most commonly used marker for the assessment of bone formation; however, since this enzyme is not found only in bone, its sensitivity and interpretation may be difficult in the assessment of bone turnover (Alper et al., 1997; Atik, 1998; Allen, 2003). Therefore, it is more accurate to evaluate bone-specific alkaline phosphatase measurements. These measurements can be performed by methods such as chemical inhibition, gel electrophoresis and heat inactivation, as well as radioimmunoassay (RIA) and enzyme-linked immunoassay (ELISA) tests (Lombardi et al., 2004).

Osteocalcin is a unique protein synthesized exclusively by osteoblasts. Osteocalcin levels are elevated when bone metabolism is accelerated. It can be used to determine the rate of bone turnover under conditions where bone destruction and bone formation are in balance; when this balance is disturbed, it is an important biochemical marker of the bone formation process. Serum osteocalcin

concentrations can be measured by Radioimmunoassay (RIA) and Enzyme Linked Immunosorbent Assay (ELISA). Other degradation products of osteoclastic bone resorption resulting from collagen degradation include pridinoline and deoxypridinoline. These parameters can be monitored by ELISA test. Pridinoline can be measured in both serum and urine, whereas deoxypridinoline can only be detected in urine (Allen, 2003).

Type 1 collagen consists of procollagen found in bone and composed of two a-1 and one a-2 collagen polypeptides containing hydroxyproline and hydroxylysine. These biochemical parameters can be measured in both serum and urine by ELISA. When the procollagen molecule is released from osteoblasts, PINP and PICP, which are formed by the cleavage of amino and carboxy-terminal ends by extracellular endoproteinases, are indicators of collagen synthesis in the bone formation process. These parameters can be detected in serum using sensitive methods such as RIA and ELISA. These assays are critical in the assessment of bone turnover and bone health (Allen, 2003).

Calcium and phosphorus levels are also among the parameters used in the assessment of bone turnover. However, the validity of these parameters is considerably lower than the previously mentioned biochemical markers. In osteoporosis, serum calcium (Ca) and phosphorus (P) levels are usually at or near normal levels. However, 24-hour urinary calcium excretion may be slightly increased (Atik, 1998). This condition is associated with an increase in the amount of calcium passing into the urine as a result of increased bone destruction.

Table 1. Biochemical indicators of bone turnover and measurement (Vik et al., 2005)

Indicator	Method	Authenticity	Prevalence of Use
Total ALP	Colorimetric	(-)	(++++)
Bone ALP	ELISA	(+++)	(++)
PICP/ PINP	RIA	(+++)	(++)
Osteocalcin	RIA, ELISA	(+++)	(+++)
Hyp	Colorimetric	(+)	(++)
Total Pyridinoline	HPLC	(++)	(+)
Free DPD	ELISA	(+++)	(+++)
NTx	ELISA	(+++)	(+++)
CTx	ELISA	(++)	(++)

11. Imaging methods

Early diagnosis of osteoporosis before fracture is usually made by Bone Mineral Density (BMD) measurements. DEXA systems are used to measure trabecular and cortical bone mineral density at various anatomical sites and this method is currently considered the gold standard (Marcus, 1996; Parfitt, 2002).

The methods used in the diagnosis of osteoporosis are as follows:

Skeletal X-rays (not suitable for early diagnosis), Morphometric X-ray Absorption Measurement, Microradioscopy, Computed Tomography, Magnetic Resonance Imaging (MRI), Measurement of Bone Mineral Density (Dual Energy X-ray Absorptiometry - DEXA) (Bartl et al., 2006; Çarlı, 2012).

12. Biomechanical properties of bone

Biomechanics is a branch of science that studies the effects of internal or external forces on living systems using engineering methods. Bone biomechanics, an important sub-branch of this discipline, specifically evaluates the fragility and

strength properties of bone. The mechanical strength and fracture propensity of bone is the result of a complex interaction of bone mass or density, architecture/geometry and the material properties of the bone matrix. None of these factors alone is sufficient to fully describe bone strength. For example, a bone with a high mineral density, with its strong but rigid structure, cannot adequately absorb external mechanical energy and therefore tends to fracture at higher forces but in a shorter time. This shows that the brittleness and fracturability of bones are related to their density, geometry and genetic makeup. The combination of these parameters in different proportions determines the fragility of a normal bone (Kutsal, 2004).

Various mechanical tests are applied to evaluate the mechanical suitability of bone. These tests allow bone to be classified as weak or strong, ductile or brittle according to its mechanical properties. To define the fragility of bone from a biomechanical point of view, three key components are usually considered; endurance or strength, frangibility or deformability, and the amount of energy the bone can withstand before fracture. These parameters are measured by biomechanical tests including compression, tensile and shear forces performed in the laboratory (Turner, 2002).

When standard tensile, compression or torsion tests are applied to any bone, they yield values that vary depending primarily on the geometry of the bone. For example, when mechanical tests are applied to bones of different sizes, the fact that the force required to break a larger bone is higher than that required to break a smaller bone does not necessarily indicate that the bone is more durable. Therefore, the true strength of the bone is determined by calculating the force per unit area. As a result, terms such as force, strain, stiffness and energy absorption are used when evaluating the geometry of the bone (organ level), while terms such as strength, stress, strain, elastic modulus and toughness are preferred at the tissue level (Turner, 1993). In mechanical tests on bone samples, a stress-strain graph similar to the load-deformation graph is obtained, which reflects the mechanical behavior of the bone material under applied loads. Stress refers to the internal force intensity generated by the load applied to the bone and is calculated by dividing this force by the applied area. Strain is the ratio of the amount of deformation to the original length. The slope of the elastic region in the stress-strain curve is called the elastic modulus and indicates the resistance of the bone material to deformation. Furthermore, the area under the curve in the stress-strain graph indicates the strength of the bone and represents the amount of energy that the bone can withstand fracture up to the fracture point (Bouxsein, 2001; Bouxsein, 2005).

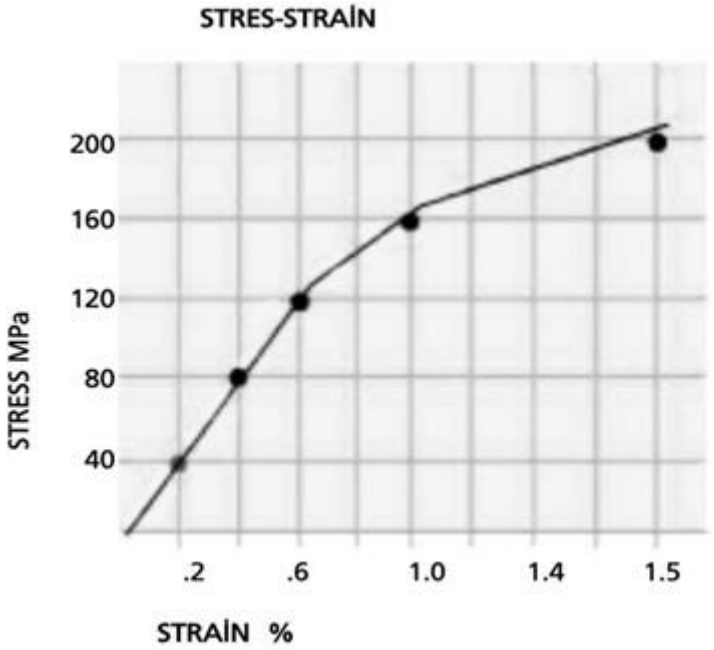

Figure 1. Stress-strain graph (Günaydın and Karatepe, 2007).

Compression and tensile loading are among the various mechanical testing methods used to understand the effects of bending and torsional forces on bone biomechanics. In compression and tensile loading, the mechanical strength of the bone is evaluated by applying a compressive or tensile force along the long axis of the bone under study (Ubara et al., 2003). These tests are one of the basic methods to analyze the effect of forces parallel to the long axis of the bone.

Flexural loading mimics the axial and bending forces that long bones are usually subjected to under in vivo conditions due to the tilt in their mechanical axis. This loading method is widely used in biomechanical studies of long bones. During flexural loading, compressive forces are generated on the loaded side of the bone and tensile forces on the opposite side, allowing the analysis of mechanical stresses in different regions of the bone. Torsional loading is performed by rotating cylindrical long bones or bone fragments in opposite directions at both ends. This test method induces shear forces on the bone and is used to measure the torsional strength of bones (An et al., 2000).

While multiaxial loading is not widely used due to the technical difficulties in their application, uniaxial loading of a bone under in vivo conditions is extremely rare. For this reason, multiaxial loading has become more preferred in recent years.

For example, while compressive loading is applied to a bone, tensile loading is simultaneously applied in different axes with models formed by muscles adhering to the bone. These multiaxial loadings help to more accurately simulate the real-world loading conditions of bones (Shahar et al., 2003).

Other test methods include traditional mechanical testing as well as a variety of specialized test methods such as indentation testing, pure shear testing, fatigue testing, acoustic testing, and micro- and nano-testing. These tests are less common than conventional tests and have been developed to meet more specific research requirements (Turner, 1993; Corwin, 2001).

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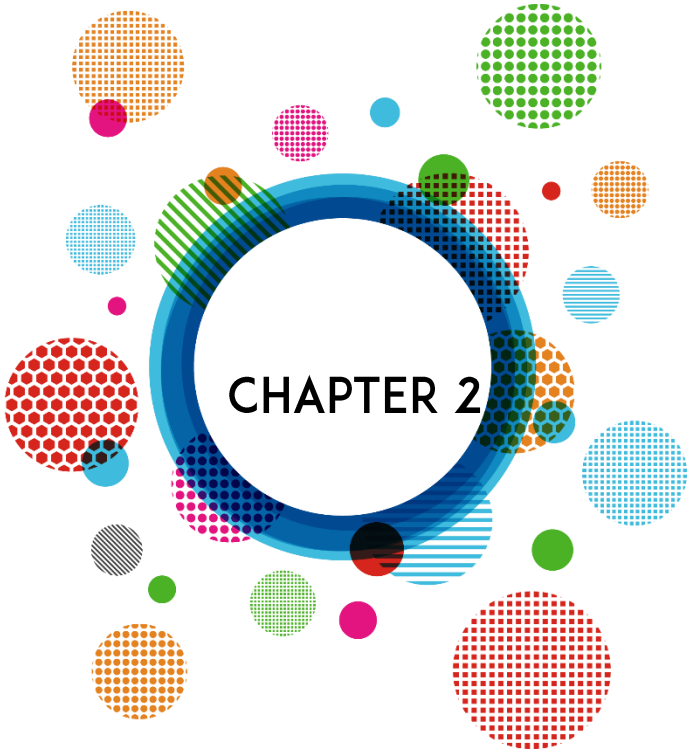

The Effects of War on Children, The Health Problems They Experience and Solution Methods

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Introduction

War disrupts the physical, psychological and social health of individuals and increases mortality and morbidity all over the world (Turkay, 2014). As a result of armed conflicts, homes are destroyed, families are separated and communities are fragmented. War breaks the sense of trust in people's relations with each other and disrupts health and education services. For children, their basic way of life is damaged. Children who cannot access basic needs such as water, food, fuel, electricity or medical supplies due to wars are forced to struggle for life in hunger, inadequate housing conditions, disease and poverty (Aydın, 2014). Lack of sufficient water and food, attack, captivity, physical torture, physical damage, witnessing torture and rape, witnessing people dying and being injured, being exposed to gunfire and explosions are the problems that children may face in wars (Layne et.al., 2010).

War draws children to the center of the incident by raping, killing, orphaning them while they are studying at school, sleeping in their beds, or playing games in a way that does not befit their innocence (Çakırer and Sirkeci, 2016). It also uses the curious, obedient and sometimes courageous nature of children to make them the subjects of war and to take their place on the front lines, paving the way for the concept of 'child soldiers' (Gözübüyük et al., 2015; Bilgin, 2014). Although the International Criminal Court has declared the recruitment of children under the age of 15 illegal as a war crime, children are still at the center of conflicts (UNICEF, 2018; Deveci, 2014). In fact, it is known that the number of children drawn to the center of the war in Syria was three times higher in 2017 than in 2015 (UNICEF, 2018).

Effects of War

Physical effects of war on children: Study on the physical effects of war on children as a result, a study was reached. Odangkara and Mpora (2014) living in rural and urban areas, Menarche status of middle school female students aged 12-18 years analyzed. As a result of the study, the average age at menarche 13.6±1.3 in rural areas and 13.3±1.4 in urban areas ($p<0.05$). At the mean age of menarche, the father's education status; no education 13.65±1.15, primary school 13.19±1.3 and 13.43±1.34 in secondary school ($p<0,05$). Mean hip circumference in girls living in rural areas 91.95±5.57, while 93.49±6.60 for those living in urban areas ($p<0.05$). Mother's education level did not affect the age of menarche negatively, and the father's education level direction ($p<0.05$). Waist circumference and Body Mass Index (BMI) did not affect the age at menarche ($p>0.05$), but hip circumference had a negative effect on BMI. ($p<0.05$)

Psychological effects of war on children: Psychological effects of war on children. As a result of the review, five studies were found. Qouta et.al. (2012), intervention after TRT application PTSD symptoms and distress in men in the treated

group. A significant decrease was observed in the findings ($p<0.05$). In the study by Sriskandarajah et al. (2015), 16.4% of the children had encountered at least one war-related event in the past years. 38.4% reported that they had experienced at least one war event. It was found that 23.7% of the children had seen dead or disabled people and 21.4% had been exposed to bombardment or gunfire. 85.5% of the children stated that they had been exposed to at least one domestic violence. It was found that sexual violence experiences within the family were 3.1%. It was determined that the rate of witnessing violence within the family was 45.4%.

In the study by Kravic et al. (2013), two groups were determined: those who experienced the Serebrenista massacre (50 people) and those who experienced the massacre but did not have intense traumatic experiences (injury, loss of family or sibling) (50 people). It was found that the Serebrenista group had higher war trauma experiences than the other group ($p<0.001$), they were exposed to more trauma in childhood ($p<0.001$), they experienced more ($p<0.05$), and the group who experienced the massacre but did not have intense traumatic experiences had better academic success ($p<0.05$).

Psychosocial effects of war on children: As a result of the examination of the psychosocial effects of war on children, two studies were found. In the study by Franic et al. (2012), it was found that the unemployment status of the fathers of the boys ($p<0.01$) and girls ($p<0.05$) whose fathers were veterans was higher than those who were not. It was reported that the status of the boys whose fathers were veterans was higher than the other group in terms of owning their own homes ($p<0.001$).

In the study of Ghazi et al. (2012), the IQ levels of children affected by the war were measured. As a result of the study, the IQ level of the children was determined as 77.7%, which showed that they had a high IQ level above the 75th percentile. It was found that the environment in which children with high IQ levels lived was good and the family's income was high ($p<0.05$).

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It opens the door to different child health problems such as nutritional problems, infectious diseases, lack of access to health services, working children, child marriages and psychosocial problems (Gözübüyük et al. 2015; Deveci, 2014).

Nutritional problems: Among the basic needs of a person, nutrition is the priority that must be met. Because it is necessary for a healthy diet to be sustainable for the continuation of all biological and physiological processes (Borlu and Ener, 2017). However, the fact that refugees have to eat carbohydrate-intensive foods not only to eat healthily but also to fill their stomachs causes inadequate and unbalanced nutrition. In this case, a series of health problems such as anemia, malnutrition, diseases due to vitamin deficiencies and growth retardation occur (Altındiş, 2013).

In order to meet the basic and social needs of children in war, cash support was provided to more than 10,400 households in 2018 with the support of UNICEF as part of the fight against poverty (UNICEF, 2018). It is also known that the Republic of Turkey Ministry of Health (SB) distributed free vitamin D and iron-containing vitamin supplements to refugee children and babies (TBMM Report, 2018).

Difficulties in accessing health services: The most important obstacle to sustainable health care for war children is the difficulties they experience in accessing health services. In studies conducted with refugees, it was determined that 58% of them have difficulties in accessing health care (Turanlı and Kıvılcım, 2005). In this regard, it is recommended that nurses working in family health centers provide health consultancy to children. In this way, children will be supported to access the right health service (Gültaç et.al., 2018).

Infectious diseases: Crowded and unhygienic living conditions have made infectious diseases a significant problem among children. The fact that the most common reasons for children to apply to health institutions in our country are diarrhea (23%) and fever (18%) shows us that infectious diseases are the areas that require the fastest intervention (Korkmaz, 2014). It is extremely important to be educated about the transmission routes, care and treatment of infectious diseases. For this reason, it is recommended that children be educated with the support of their parents in addition to their health care (Gültaç et al., 2018).

Psychosocial problems: It is very difficult to compensate for the losses experienced, especially for children, and to establish a new order. Because every type of loss is painful and a cause for mourning (Gözübüyük et al., 2015). Losing or being separated from family members during the war also affects family processes, and positions and roles change within the family (Aydın et al., 2017). Children's ability to adapt to changes in their social environment, cultural structure, language and habits, and to cope with problems such as alienation is another dimension that deeply affects children's development (Özservet and Sirkeci 2016). Internet, television and playgrounds have been prepared for the social development and mental rehabilitation of children. A crèche service has been initiated for children and 6810 children have benefited from this service (TBMM Report, 2018). Approximately 200,000 children have benefited from UNICEF-supported community-based protection services and more than 90,000 children have been included in the protection and psychosocial support program (UNICEF, 2018).

Child marriages: These marriages are sometimes carried out for financial resources and sometimes for the protection of girls in the face of violence, economic and cultural problems encountered after war, migration (Akpınar, 2017; Aydın et al., 2017). Child marriages separate children from their families, schools and friends while they have not yet developed sufficiently, prevent them from completing their education and most likely expose them to domestic violence (Özcebe and Biçer,

2013). Legal and practical measures should be taken to open the way for these children to go to school, not to marriage (Christiansen and Chandra, 2013; Özcebe and Biçer, 2013). In order to prevent child marriages in our country, trainings have been organized for refugees and to date, 437 people have been informed about the issue, and their legal rights and state sanctions have been explained (TBMM Report, 2018).

Working child: War increases its destructive effect on children through the concept of working children (Erdoğan and Ünver, 2015). The social security status of children, the control of harsh and unregistered working conditions and the meeting of the increasing health needs of working children are very important issues (UNICEF, 2018). At the very least, preventing illegal working environments or providing vocational training will be a factor that reduces possible health problems. Otherwise, the cost of unstoppable child labor will negatively affect the health of children in the developmental age (Bilgin, 2009). In addition, the number of refugee children working and begging in our country, especially in big cities, is quite high (UNICEF, 2018). The state has allocated a rehabilitation camp for these children to be rehabilitated. In addition, dormitories have been established within the scope of social services for unaccompanied children. However, most of the children do not prefer to stay in these environments (TBMM Report, 2018).

Conclusion

Finally, all of humanity should feel responsible for the child in a war environment to cope with so many problems and to prepare for life. Therefore, the policies and measures taken by states and international institutions should be future-oriented rather than day-to-day. In addition, it is important to pay attention to the fact that these policies and practices primarily aim to protect children's rights and health, prevent informality, and are applicable, sustainable and auditable. From this perspective, in order for children to live a dignified and healthy life, all areas of physical, psychosocial and cognitive development of the child should be supported with a multidisciplinary approach.

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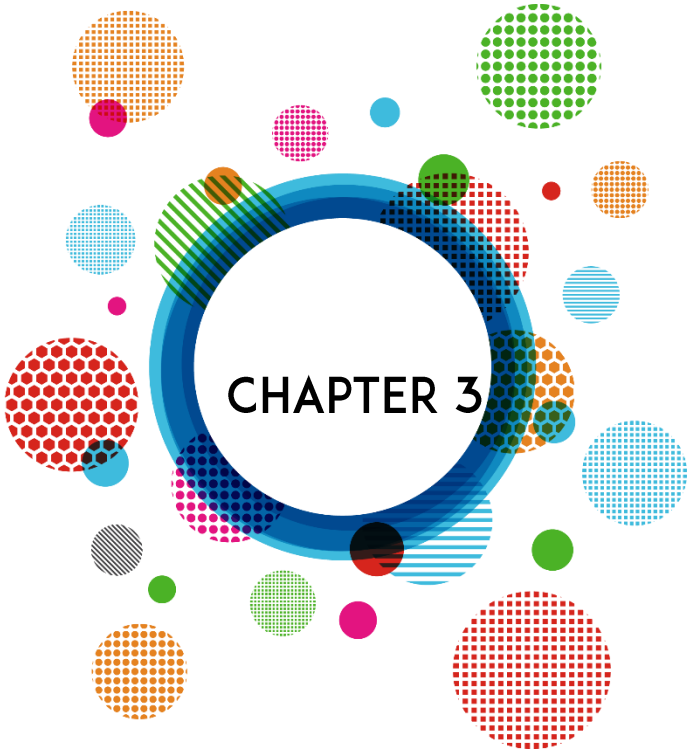

The Relationsiıp Between Cancer and Ras Mutations

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Introduction

The RAS family of small GTPases plays a crucial role in regulating cell growth, differentiation, and survival. Mutations in RAS genes result in a constitutively active GTP-bound state, leading to persistent activation of downstream effectors such as the MAPK/ERK and PI3K/AKT pathways (Prior et al., 2020). Approximately 19% of all human cancers harbor RAS mutations, with KRAS being the most frequently altered isoform (Cox et al., 2014).

Prevalence of RAS Mutations in Cancer

RAS mutations are found in a wide range of malignancies, including:

Pancreatic ductal adenocarcinoma (PDAC): ~90% of cases have KRAS mutations (Bryant et al., 2014).

Colorectal cancer (CRC): ~40-50% of cases exhibit KRAS mutations (Vogelstein et al., 2013).

Non-small cell lung cancer (NSCLC): ~30% of cases harbor KRAS mutations (Skoulidis et al., 2015).

Melanoma: ~15-20% of cases have NRAS mutations (Jakob et al., 2012).

These mutations are often associated with poor prognosis, resistance to therapy, and aggressive tumor behavior (Pylayeva-Gupta et al., 2011).

Mechanisms of RAS-Driven Oncogenesis

RAS mutations lead to:

1. **Constitutive signaling activation:** Mutant RAS remains locked in the GTP-bound state, continuously stimulating proliferation via MAPK and PI3K pathways (Downward, 2003).
2. **Metabolic reprogramming:** RAS-driven cancers exhibit increased glycolysis and glutamine metabolism (Ying et al., 2012).
3. **Immune evasion:** RAS mutations alter the tumor microenvironment, suppressing anti-tumor immunity (Canon et al., 2019).

Therapeutic Challenges and Advances

Historically, RAS was considered "undruggable" due to its high affinity for GTP and lack of deep binding pockets. However, recent breakthroughs include:

KRAS-G12C inhibitors: Sotorasib (AMG 510) and Adagrasib (MRTX849) selectively target the KRAS-G12C mutation (Hong et al., 2020).

Combination therapies: MEK and ERK inhibitors are being tested alongside RAS-targeting drugs (Moore et al., 2020).

Immunotherapy approaches: Checkpoint inhibitors show promise in RAS-mutant tumors with high tumor mutational burden (TMB) (Rizvi et al., 2015).

Pancreatic ductal adenocarcinoma (PDAC) accounts for over 90% of pancreatic cancers and remains a leading cause of cancer-related deaths worldwide, with a 5-year survival rate of only ~12% (Siegel et al., 2023). The aggressive nature of PDAC is largely attributed to late diagnosis, early metastasis, and resistance to conventional therapies. Genomic studies have identified *KRAS* as the most frequently mutated oncogene in PDAC, present in ~90% of cases (Bryant et al., 2014). Mutations in *KRAS*, particularly at codon 12 (e.g., G12D, G12V, G12R), result in a constitutively active GTP-bound state, perpetuating downstream oncogenic signaling.

RAS Mutations in Pancreatic ductal adenocancer Pathogenesis

The RAS family (*KRAS*, *NRAS*, *HRAS*) encodes small GTPases that regulate cell proliferation, differentiation, and survival. In PDAC, *KRAS* mutations (most commonly in exon 2) lock the protein in an active state, leading to persistent signaling through pathways such as:

MAPK/ERK (promoting proliferation)

PI3K/AKT (enhancing survival)

RALGEF (regulating cytoskeletal dynamics and invasion) (Pylayeva-Gupta et al., 2011)

These pathways collectively contribute to tumor initiation, progression, and therapeutic resistance. Mouse models with pancreas-specific *KRAS* mutations develop preneoplastic lesions (PanINs) that progress to invasive PDAC, underscoring its driver role (Hingorani et al., 2005).

Clinical Implications and Therapeutic Challenges

Despite its central role in PDAC, direct targeting of mutant KRAS has historically been challenging due to its high affinity for GTP and lack of deep binding pockets. However, recent advances have led to the development of:

KRAS-G12C inhibitors (e.g., sotorasib, adagrasib), though these are ineffective in PDAC due to the rarity of G12C mutations (Strickler et al., 2021).

G12D-specific inhibitors (e.g., MRTX1133), showing promise in preclinical models (Wang et al., 2022).

Combination therapies targeting downstream effectors (e.g., MEK, ERK inhibitors) or synthetic lethal interactions (e.g., autophagy inhibitors) (Bryant et al., 2019).

KRAS mutations are a defining feature of PDAC and a critical therapeutic target. While progress has been made in developing RAS inhibitors, the heterogeneity of

PDAC necessitates broader strategies, including immunotherapy and stromal targeting. Future research should focus on overcoming resistance mechanisms and identifying biomarkers for personalized therapy.

RAS mutations are key drivers of oncogenesis in multiple cancers. While therapeutic targeting remains challenging, recent advances in direct RAS inhibition and combination strategies offer new hope for patients with RAS-mutant tumors. Further research is needed to overcome resistance mechanisms and improve clinical outcomes.

Relationship Between Colorectal Cancer and RAS Mutations

Colorectal cancer (CRC) is one of the most common malignancies worldwide, with genetic alterations playing a crucial role in its pathogenesis. Among these, mutations in the RAS family of oncogenes (KRAS, NRAS, and HRAS) are frequently observed and significantly influence tumor behavior, therapeutic response, and prognosis. This review explores the prevalence, molecular mechanisms, and clinical implications of RAS mutations in CRC, emphasizing their role in resistance to anti-EGFR therapies and potential therapeutic strategies.

Colorectal cancer remains a leading cause of cancer-related morbidity and mortality, with over 1.9 million new cases diagnosed annually (Sung et al., 2021). The RAS family of GTPases (KRAS, NRAS, and HRAS) regulates critical cellular processes, including proliferation, survival, and differentiation. Mutations in these genes lead to constitutive activation of downstream signaling pathways, such as MAPK/ERK and PI3K/AKT, promoting tumorigenesis (Prior et al., 2020). Approximately 40–50% of CRC cases harbor KRAS mutations, while NRAS mutations occur in 3–5% of cases (Benson et al., 2021).

Prevalence and Molecular Subtypes of RAS Mutations in CRC

The most common RAS mutations in CRC occur in KRAS codons 12, 13, and 61, with G12D, G12V, and G13D being frequent substitutions (Cox et al., 2014). NRAS mutations, though less common, are predominantly found in codon 61 and are associated with similar oncogenic effects.

RAS mutations are more prevalent in left-sided (distal) colon cancers compared to right-sided (proximal) tumors, which often exhibit microsatellite instability (MSI) or BRAF mutations (Missiaglia et al., 2014). This distinction has therapeutic implications, as RAS-mutant tumors typically show resistance to EGFR inhibitors (e.g., cetuximab and panitumumab) (De Roock et al., 2010).

Role of RAS Mutations in CRC Progression and Therapy Resistance

1. Impact on EGFR-Targeted Therapies

The presence of RAS mutations is a well-established predictive biomarker for resistance to anti-EGFR monoclonal antibodies (Van Cutsem et al., 2011). The CRYSTAL and PRIME trials demonstrated that only RAS wild-type patients benefit from cetuximab or panitumumab (Douillard et al., 2013; Bokemeyer et al., 2016). Consequently, RAS testing is now mandatory before initiating EGFR-targeted therapy in metastatic CRC (mCRC).

2. Alternative Signaling Pathways and Therapeutic Vulnerabilities

Despite resistance to EGFR inhibitors, RAS-mutant CRCs may still respond to:

MEK inhibitors (e.g., trametinib), though with limited efficacy (Kopetz et al., 2017).

Combination therapies targeting downstream effectors (e.g., ERK or PI3K inhibitors).

Immunotherapy in **MSI-high (MSI-H) RAS-mutant CRC**, where PD-1 inhibitors (pembrolizumab/nivolumab) show benefit (Le et al., 2017).

Emerging Strategies for Targeting RAS-Mutant CRC

Recent advances in **direct RAS inhibition**, such as the **KRAS G12C inhibitor sotorasib**, have shown promise in other cancers (e.g., NSCLC) but remain under investigation in CRC (Hong et al., 2020). Additionally, **synthetic lethality approaches** (e.g., targeting metabolic dependencies in RAS-mutant cells) are being explored.

Prevalence of RAS Mutations in Melanoma

NRAS mutations occur in **15–20%** of melanomas, predominantly at codon 61 (Q61K/R/L), leading to constitutive activation (Cancer Genome Atlas Network, 2015).

KRAS and HRAS mutations are less common but have been identified in subsets of melanomas (Fedorenko et al., 2016).

NRAS-mutant melanomas are often associated with:

- **Chronic sun-damaged skin** (CSD) (Shain et al., 2015).
- **Nodular and aggressive subtypes** (Jakob et al., 2012).
- **Resistance to BRAF inhibitors** when co-occurring with BRAF mutations (Johnson et al., 2015).

Mechanisms of RAS-Driven Melanomagenesis

1. **Constitutive MAPK Pathway Activation**
    - Mutant NRAS sustains **ERK signaling**, promoting uncontrolled proliferation (Dankort et al., 2009).
2. **PI3K/AKT/mTOR Pathway Activation**
    - NRAS mutations enhance **AKT signaling**, contributing to cell survival and therapy resistance (Kwong et al., 2012).
3. **Crosstalk with Other Oncogenic Pathways**
    - Interaction with **CDK4/6** and **MITF** amplifies melanoma growth (Goydos et al., 2005).

Clinical Implications and Therapeutic Challenges

NRAS-mutant melanomas are associated with **poorer prognosis** and limited targeted therapy options (Devitt et al., 2011).

MEK inhibitors (e.g., trametinib, binimetinib) show partial efficacy but face resistance (Ascierto et al., 2013).

Combination therapies (MEK + CDK4/6 inhibitors) are under investigation (Kwong et al., 2015).

Immunotherapy (anti-PD-1/CTLA-4) remains a key treatment due to high tumor mutational burden (Snyder et al., 2014).

Prognostic Impact of RAS Mutations in NSCLC

1. KRAS Mutations and Survival Outcomes

The prognostic role of *KRAS* mutations in NSCLC has been extensively studied, with divergent findings. Some studies suggest that *KRAS* mutations are associated with poorer overall survival (OS) and progression-free survival (PFS), particularly in advanced-stage disease (Meng et al., 2013). However, other reports indicate that *KRAS* mutations may not independently affect prognosis but instead influence treatment response (Ihle et al., 2012).

Subtype-specific differences also play a critical role. The *KRAS* p.G12C mutation, found in ~13% of NSCLC cases, has been linked to aggressive disease and resistance to chemotherapy (Arbour et al., 2018). Conversely, non-G12C mutations (e.g., G12D, G12V) may have different prognostic implications, though further validation is needed (Skoulidis et al., 2015).

2. NRAS and HRAS Mutations

While *KRAS* mutations dominate in NSCLC, *NRAS* and *HRAS* mutations are rare (<1%) and their prognostic significance remains poorly understood (Reck et al., 2016). Limited data suggest that *NRAS* mutations may confer resistance to EGFR tyrosine kinase inhibitors (TKIs), while *HRAS* mutations are associated with squamous cell carcinoma histology (Riely et al., 2009).

Therapeutic Implications and Resistance Mechanisms

Historically, *RAS*-mutant NSCLC has been considered difficult to target due to the lack of effective direct inhibitors. However, recent advances, such as the development of *KRAS* G12C inhibitors (e.g., sotorasib, adagrasib), have shown promising clinical activity (Hong et al., 2020; Jänne et al., 2021). Despite these breakthroughs, resistance mechanisms, including secondary *RAS* mutations and activation of bypass pathways, remain a challenge (Awad et al., 2021).

Combination therapies targeting downstream effectors (e.g., MEK, ERK inhibitors) or immune checkpoint inhibitors (ICIs) are being explored, as *KRAS*-mutant tumors often exhibit a higher tumor mutational burden (TMB) and may respond better to immunotherapy (Dong et al., 2020).

RAS mutations, particularly in *KRAS*, significantly influence NSCLC biology and prognosis, with mutation-specific effects on survival and treatment response. The advent of *KRAS* G12C inhibitors marks a turning point in targeted therapy, yet further research is needed to elucidate the prognostic heterogeneity among different *RAS* mutations and optimize therapeutic strategies.

Conclusion

RAS mutations are key drivers of oncogenesis in multiple cancers. While therapeutic targeting remains challenging, recent advances in direct RAS inhibition and combination strategies offer new hope for patients with RAS-mutant tumors. Further research is needed to overcome resistance mechanisms and improve clinical outcomes. On the other hand RAS mutations are a key driver of CRC progression and a major determinant of therapeutic resistance. While anti-EGFR therapies are ineffective in RAS-mutant CRC, ongoing research into direct RAS inhibitors and combination strategies offers hope for improved outcomes. Routine RAS genotyping remains essential for personalized treatment in mCRC. RAS mutations, particularly in NRAS, are key drivers of melanoma progression and therapeutic resistance. While targeted therapies for RAS-mutant melanomas remain limited, ongoing research into combination strategies and immunotherapy offers hope for improved outcomes RAS mutations, particularly in KRAS, significantly influence NSCLC biology and prognosis, with mutation-specific effects on survival and treatment response. The advent of KRAS G12C inhibitors marks a turning point in targeted therapy, yet

further research is needed to elucidate the prognostic heterogeneity among different RAS mutations and optimize therapeutic strategies.

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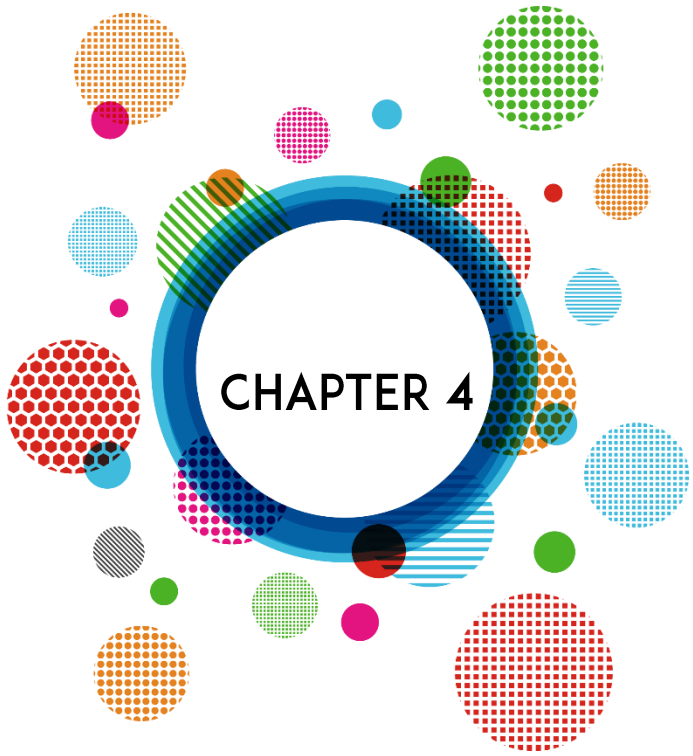

Irritable Bowel Syndrome: Current Approach

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Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits[1]. It's clear that this issue is not only driving up health care costs, but also leading to a significant rise in work absenteeism, ranking as the second highest cause[2,3].

EPIDEMIOLOGY

A meta-analysis of eight international studies clearly shows that the pooled prevalence of IBS is 11%, with significant variations by geographic region[4].

The prevalence of the disease was evaluated according to age, and the results were clear: it was 25% lower in people older than 50 years compared to younger people[5]. The literature clearly shows that the prevalence of IBS in women has increased more than in men in recent years[6]. However, a recent study has revealed that in Asian countries, IBS is equally prevalent in men and women[7,8,9]. The disease is prevalent among educated, affluent individuals, students, and young people[10].

PATHOPHYSİOLOGY AND EPIDEMİOLOGY

While the exact cause of IBS is still unclear, it is believed to be the result of several factors interacting. These factors are as follows:

a) Abnormal gastrointestinal motility:

Motility abnormalities such as irregularity of luminal contractions, prolonged transit time in IBS with constipation, and exaggerated motor response to cholecystokine and food intake in IBS with diarrhea predominance are seen in IBS, but a general disease-specific motility pattern has not been defined[11-15]. In addition, pharmacologic stimulation of bowel motility in IBS patients has been reported to reduce gas retention and improve symptoms[16].

b) Visceral hypersensitivity:

Sensation in the gastrointestinal tract is caused by stimulation of various receptors in the intestinal wall. These receptors transmit signals via afferent nerve pathways to the dorsal horn of the spinal cord and ultimately to the brain. Visceral hypersensitivity (increased response to stimuli such as tension and pressure) is a common finding in IBS patients. Recognition of these interactions has led to the concept that IBS is a "brain-gut axis disorder", a term that has now replaced the earlier term "functional bowel disorder"[17].

c) Intestinal Inflammation:

Immunohistological examinations in diarrhea-dominant IBS patients and postinfectious IBS patients indicate mucosal immune system activation characterized by changes in certain immune cells and markers. These changes can be seen as increased number of lymphocytes in the colon and small intestine,

increased lymphocyte infiltration in the myenteric plexus, and neuronal degeneration[18].

Increased lymphocytic cells secrete nitric oxide, histamine, and proteases. These can stimulate the enteric nervous system, leading to abnormal motor and visceral responses in the intestine. Stool examinations from IBS patients with predominant diarrhea have revealed high levels of serine-protease activity[19,20].

Studies have shown that plasma levels of proinflammatory cytokines are increased in IBS patients. Mononuclear cells in peripheral blood produce more tumor necrosis factor (TNF) than healthy individuals[21,22].

Studies definitively show that mast cells, which are key players in the immune system, are increased in the terminal ileum, jejunum, and colon regions of IBS patients. This increase is strongly correlated with abdominal pain in IBS[23,24].

d) Post-infectious period:

Some people diagnosed with IBS experience diarrhea before the onset of symptoms. This has led to the need to understand the post-infectious causes of IBS. Studies have shown that bacterial, protozoan, helminth, and viral infections pave the way for IBS[25-29].

IBS is four times more common in people with a history of acute gastroenteritis, and symptoms continue in almost 40% of patients even after five years. Young age, female gender, history of anxiety, diarrhea lasting longer than three weeks, and the need for hospitalization are the risk factors for post-infectious IBS[30].

e) Change in Stool Microbiota:

Studies show that the stool microbiota in individuals with IBS is different from healthy controls and varies according to the dominant symptom. Probiotics' gas- and bloating-reducing effect in IBS further supports the idea that changes in the microbiota may play a role in its etiology[31].

Bacterial Overgrowth: Small intestinal bacterial overgrowth (SIBO) is a dysbiosis of the gut microbiota associated with an increased number and/or type of bacteria in the upper gastrointestinal tract, which is quite common in patients with IBS[32]. Studies that support the link between SIBO and IBS have IBS patients take a small amount of a carbohydrate, and then their breath is checked for unusual hydrogen levels. Studies have shown that getting rid of SIBO can help with IBS symptoms[33-35]. Studies that do not support this relationship suggest that abnormal breath tests detected in patients with IBS may be due to accelerated orocecal transit in patients with IBS rather than SIBO[36,37]. In addition, treating patients with IBS with proton pump inhibitors often is also a risk factor for developing SIBO[38]. So, we can't say for sure what causes what in these two conditions.

a) **Food intolerance:** The role of food in the pathophysiology of IBS remains ambiguous. Research indicates that between 45% and 60% of patients diagnosed with IBS report a worsening of symptoms following the ingestion of food, with this effect being more pronounced when certain foods are consumed. Research examining the impact of food on IBS has predominantly centered on food-specific antibodies, carbohydrate malabsorption (particularly fructose intolerance), and gluten sensitivity[39-41].

One postulation regarding the etiology of IBS suggests a potential correlation between symptoms and impaired carbohydrate absorption. The theory posits that in patients diagnosed with IBS, fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs) reach the distal small intestine and colon. In these regions, the FODMAPs undergo fermentation, a process that has been shown to induce symptoms, elevate intestinal permeability, and potentially trigger inflammation[42].

Individuals diagnosed with celiac disease, which is characterized by gluten hypersensitivity, frequently exhibit IBS-like symptoms. Research has indicated that adopting a gluten-free diet can alleviate IBS symptoms[43].

b) **Genetic predisposition:** The association of specific genes with IBS is currently under investigation. Genotyping studies have demonstrated an association between IBS and serotonin transporter gene polymorphism, which has been shown to affect intestinal peristalsis[44,45]. In the context of twin studies, while there are studies that demonstrate the disease's compatibility with genetic transmission, with a higher prevalence observed in identical twins compared to fraternal twins, there are also studies that do not substantiate this association[46,47]. Another intriguing study demonstrated that having a parent with IBS served as a more significant predictor than having a twin sibling with IBS. This is a striking result, indicating that RLS may be caused by social learning as well as familial characteristics[48].

Psychosocial factors: According to Locke and Solmaz's report, individuals diagnosed with IBS appear to demonstrate heightened levels of anxiety, depression, phobia, and somatization, in addition to experiencing elevated levels of daily stress when compared to a control group[49,50]. A growing body of research has identified psychosocial factors, including anxiety, sleep disturbances, and somatic symptoms, as independent risk factors for the development of IBS in individuals who have not previously been diagnosed with IBS[51].

Clinical: The IBS clinic can present with a wide range of symptoms, both gastrointestinal and extraintestinal[52].

a. Gastrointestinal System Findings:

- Chronic abdominal pain with variable frequency and periodic exacerbations
- Diarrhea attacks only
- Constipation attacks only
- Alternating episodes of diarrhea and constipation
- A clinical alternation between diarrhea-constipation-normal bowel habits
- Diarrhea characterized by frequent loose stools of small to medium volume
- Usually hard, pellet-shaped stools
- Tenesm
- Intermittent prolonged constipation

b. Findings outside the gastrointestinal tract:

- Sexual dysfunction,
- Dysmenorrhea
- Dyspareunia
- Increased urinary frequency and sudden need for micturition
- Fibromyalgia

DIAGNOSIS

The first step in diagnosing IBS is taking a detailed medical history. In the anamnesis, the patient's use of diarrhea or constipating medication should be questioned. Physical examination is usually normal in IBS patients. Mild abdominal tenderness may be detected by palpation in some patients[53,54].

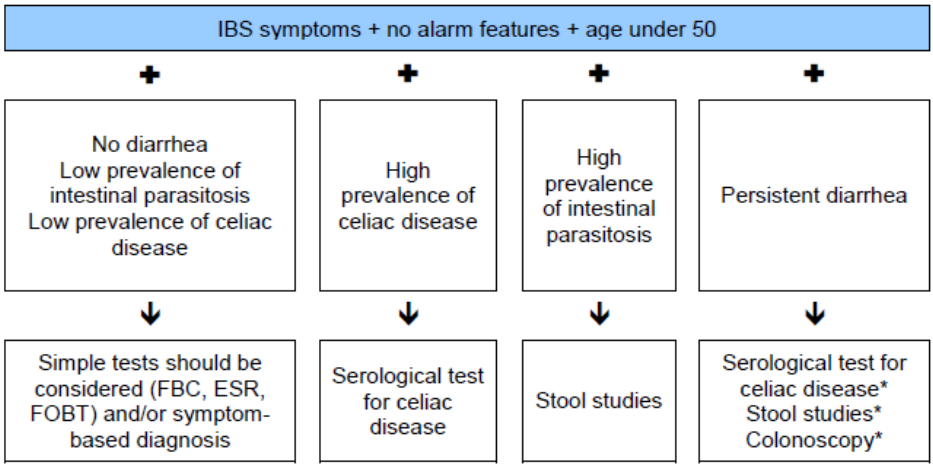
A clinical situation without abdominal pain excludes the diagnosis of IBS. Abdominal pain in IBS often occurs in the lower abdomen. Constipation or diarrhea accompanies the abdominal pain and relief is seen after defecation. The presence of varying patterns of defecation more than three times a week suggests diarrhea predominant type of IBS. Absence of defecation for several days in a row suggests constipation predominant type IBS. Symptoms such as abdominal distension, feeling of tightness, excessive straining during defecation, fecal incontinence are not specific for the diagnosis of IBS but are symptoms observed in many patients[55,56].

The most widely used diagnostic criteria in the diagnosis of IBS are the Rome IV criteria. **ROME IV Criteria[57,58]:**

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool a Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

The IBS diagnostic diagram is illustrated in figure 1.



Notes: ESR, erythrocyte sedimentation rate; FBC, full blood count; FOBT, fecal occult blood test.

Esophagogastroduodenoscopy and small intestinal biopsy for enteropathy, giardiasis, and changes associated with small-intestinal bacterial overgrowth (SIBO) may be recommended in high-resource areas in selected cases

* Where relevant—i.e., when there is a high prevalence of celiac disease, parasitosis, inflammatory bowel disease, or lymphocytic colitis.

Figure 1. The IBS diagnostic diagram. Resource:59

CLASSIFICATION: IBS subtypes are determined by the dominant bowel habit reported by the patient on days when bowel movements are abnormal. The Bristol stool scale (BSFS) (Figure 2) is used to assess stool consistency. The patient should not be taking bowel regulators at the time of assessment[60].

- IBS with constipation predominance (IBS-C): Patient reports that abnormal bowel movements are usually constipation (types 1 and 2 on the BSFS)

- IBS with diarrhea predominance (IBS-D): Patient reports that abnormal bowel movements are usually diarrhea (types 6 and 7 on the BSFS)

- **IBS with mixed bowel habits (IBS-M)**: Patient describes abnormal bowel movements as periods of constipation and diarrhea

- **Unclassified IBS (IBS-U):** Patients who meet the diagnostic criteria for IBS but whose subtype cannot be accurately categorized.

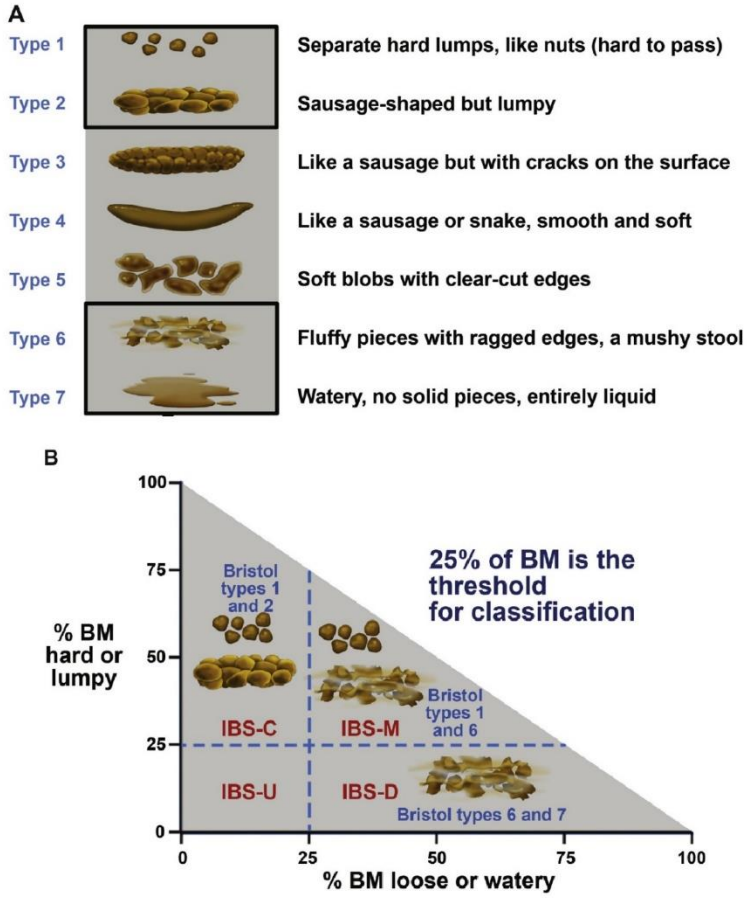


Figure 2. (A) Bristol Stool Form Scale (BSFS) (B) IBS subtypes are determined according to stool consistency using BSFS. Resource: 58

Alarm features:

•Age of onset after age 50 years

•Rectal bleeding or melena

•Nocturnal diarrhea

•Progressive abdominal pain

•Unexplained weight loss

•Laboratory abnormalities (iron deficiency anemia, elevated C-reactive protein or fecal calprotectin/lactoferrin)

•Family history of irritable bowell disease or colorectal cancer

The presence of alarm symptoms suggests the possibility of organic disease. However, most patients with alarm symptoms do not have an organic disease[61].

TREATMENT

The primary process for treatment approaches is the establishment of a reliable patient-physician relationship. Because IBS requires close follow-up and a holistic approach to treatment[62,63].

Historically, IBS has been associated with stress and anxiety, and a brain-gut axis IBS relationship has been identified. As such, many treatments have focused on antidepressants and neurobehavioral interventions. While these treatments can be effective, more recent studies have shown complex, gut-specific organic etiologies and new treatment modalities are being sought. The complex web of etiologies requires the identification of a variety of patient-specific pathophysiologic conditions. These include visceral hyperalgesia, increased intestinal permeability, activation of autoimmune mechanisms, impaired gastrointestinal motility and changes in the gut microbiota. The gut microbiota has become a focus of interest in the treatment of IBS in recent years[63-65].

The patient should be informed that there is currently no definitive treatment for IBS, that the disease is chronic, and that the prognosis is good. It should be emphasized that IBS treatment is for symptom relief only. This information will help set realistic goals and keep the patient's expectations at a reasonable level[66].

1. Lifestyle Changes and Diet:

Exercise has been shown to reduce IBS symptoms, so regular physical activity is recommended for people with IBS. A randomised study found that 12 weeks of increased physical activity (20 to 60 minutes of moderate activity, three to five days a week) was associated with improvements in IBS symptoms, compared with maintaining current activity[67].

Sleep disturbance is common in patients with IBS and is associated with symptoms[68-70]. Sleep hygiene recommendations should be given to these patients (regular bedtime and rise time, avoid napping, limit caffeine and alcohol, avoid nicotine, keep the sleep environment quiet and dark, avoid evening eating etc.) and the use of medications that interfere with sleep hygiene should be reviewed. Melatonin has become an alternative treatment for IBS because it plays a role in gastrointestinal motility and is often used as a sleep aid[70,71]. In a study of 136 patients

with IBS, daily melatonin supplementation improved sleep quality, abdominal pain and quality of life at follow-up[71].

All patients with IBS should be offered first-line dietary advice[72]. General recommendations for a dietary approach in IBS are: regular meal consumption, adequate fluid intake, avoidance of alcohol, caffeine, carbonated drinks and spicy foods that can trigger symptoms, and increased physical activity[73]. Patients with IBS should make a habit of taking time for meals, not skipping meals, eating sitting down, chewing food thoroughly and not eating late at night[74].

Nutritional therapy is one of the most important options for IBS. Foods associated with the patient's symptoms should be eliminated or reduced from the diet. Adequate fluid intake should be maintained; small, frequent meals should be eaten[75]. Symptoms such as bloating, abdominal pain and diarrhea can be prevented with a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, polyhydric alcohols) diet[76].

a.Low-FODMAP Diet

FODMAPs, "Fermentable Oligo-, Di- and Mono-saccharides and Polyols", are a group of highly fermentable but poorly absorbed short-chain carbohydrates and polyols that are commonly found in various vegetables and fruits, wheat and cereal groups, dairy products, legumes and sweeteners[55,77,78].

In 7 out of 10 patients with IBS, symptoms of bloating and pain are triggered by FODMAPs. Since FODMAPs are not fully absorbed in the small intestine, they retain water and ferment in the colon, leading to distension and abnormal motility and the production of short-chain fatty acids[79]. In IBS patients with visceral hypersensitivity, dietary FODMAP restriction has been associated with symptom improvement[80].

One version of a low FODMAP diet involves restricting FODMAP intake for 4-8 weeks, followed by gradual reintroduction based on tolerance. Personalized programs are important because adherence to the FODMAP diet is difficult over the long term[81,82]. However, this dietary model is not appropriate for individuals at risk for nutritional deficiencies and those with psychologically active eating disorders[80]. The list of foods allowed and prohibited in the low-FODMAP diet is shown in Figure 3.

Food Categories	Allowed Foods	Forbidden Foods
Cereals	Rice, porridge, oats, quinoa, tapioca, millet, amaranth, buckwheat, gluten-free bread and cereals, potato-flour.	Bread and bakery products, biscuits, croissants, pasta, wheat flour, Kamut, barley, rye, couscous, flour, muesli.
Milk and derivates	Lactose-free milk, rice milk, oat milk, soy milk and all vegetable drinks, yogurt lactose free, soy yogurt, Greek yogurt, hard cheeses, fruit sorbets.	Cow milk, goat milk, yogurt with lactose, fresh cheeses, butter, ice cream, cream.
Vegetables	Carrot, pumpkin, Chinese cabbage, celery, lettuce, spinach, potato, tomato, zucchini, eggplant, green bean, beets, red pepper, herbs, olives, bamboo shoot, fresh herbs.	Asparagus, cauliflower, garlic, onion, shallot, mushroom, leek, chicory, fennel, artichoke, Brussel sprout, broccoli, radish, pepper, turnips.
Legumes	Peas, soy products.	Beans, chickpeas, lentils, soybeans.
Fruit	Banana, blueberry, strawberry, raspberry, grape, melon, grapefruit, kiwi, orange, lemon, limes, pineapple, passion fruit.	Apple, pear, watermelon, mango, apricot, avocado, cherry, peach, plum, persimmon, lychee, fruit juices.
Dried fruits	Almonds, hazelnuts, walnuts, pine nuts.	Pistachios, cashews.
Sweeteners	White sugar, brown sugar, maple syrup.	Agave, honey, fructose, xylitol, maltitol, mannitol, sorbitol.

Figure 3. Foods Allowed and Prohibited on a Low FODMAP Diet. Source:77

In addition to relieving IBS symptoms, a low FODMAP diet should be initiated and followed by specialists in the field, as it can lead to inadequate fiber, iron, and calcium intake and a decrease in beneficial bacteria in the intestinal flora[79,83,84]. One study recommended the use of probiotics during the diet to overcome the negative effect of a low FODMAP diet on the gut microbiota[85].

b. Gluten-free diet: There are studies showing that a gluten-free diet has a positive effect on symptoms and bowel habits in controlling IBS symptoms[86]. In a prospective study of 50 patients with IBS, a high response to a gluten-free diet was observed, particularly in patients with high levels of antigliadin A and antigliadin G. A decrease in diarrheal symptoms was observed in a quarter of patients with negative antigliadin antibodies[87]. There are also studies showing that a gluten-free diet does not work in irritable bowel syndrome[88]. The British Society of Gastroenterology does not recommend a gluten-free diet for IBS[72].

c. Lactose-free diet: The incidence of lactose malabsorption in patients with IBS is the same as in the healthy population. However, patients with IBS and lactose intolerance may have an exaggerated symptom response to lactose intake[89]. Some patients with misdiagnosed IBS may have undiagnosed lactose intolerance. In such patients, a lactose-restricted diet may provide sustained relief[61,90,91].

d. Nutritional Supplements:

i. Enteric-coated peppermint oil: Peppermint oil may be a good treatment option for abdominal pain. It works through direct antimicrobial and anti-inflammatory effects, relief of psychological distress, and smooth muscle relaxation. As an herbal treatment, peppermint oil formulations and dosages may vary (0.2 ml orally 3 times daily or 180 mg 3 times daily; may be titrated up to 0.4 ml or 360 mg orally 3 times daily). Enteric-coated or encapsulated formulations allow the active ingredient to be released in the small intestine[92]. Gastroesophageal reflux is a common side effect of peppermint oil use[72].

ii. Probiotics: Although probiotics may be effective for general symptoms and abdominal pain in IBS, no specific type or strain can be recommended. Patients who want to try probiotics should take them for up to 12 weeks and stop if symptoms do not improve[72].

iii.Fibre Intake

Fiber intake can be used to treat constipation-predominant irritable bowel syndrome (IBS-C). Water-soluble fibers (such as pysillium) relieve symptoms and are as effective as many pharmacological treatments[93]. Soluble fibre sources, such as ispaghula husk, are an effective treatment for the general symptoms and abdominal pain of IBS, but insoluble fibre (e.g. wheat bran) should be avoided as it may worsen symptoms. As some patients may experience increased bloating and gas, soluble fibre should be started at a low dose (3-4 g/day) and increased over time. For commercial fibre products, the product-specific label should be checked to determine the dosage[72].

1. **Medical Treatment:** Pharmacotherapy may be added to treatment for patients whose symptoms persist despite lifestyle and dietary changes. Treatment varies according to the type of IBS[94].

i. **<u>IBS-C Treatment:</u>** In the absence of studies directly comparing treatment options, treatment choice is based on patient preferences, symptoms, and side effect profiles. Agents can be administered sequentially to determine the treatment regimen that provides optimal relief[94].

   a. **Polyetilen Glycol(PEG):** PEG, an osmotic laxative, is the agent of first choice in constipation-predominant IBS. The medication is affordable and generally well-tolerated. In comparison with other osmotic laxatives, it has

a reduced incidence of adverse effects. The treatment is initiated with a dosage of 17 g of the powder, dissolved in one cup (8 ounces) of water, administered once daily. The dosage may be increased to a maximum of 34 g per day, contingent upon the patient's individual response to the treatment. It is important to note that adjustments in dosage may be made at intervals of two to three days, until the desired level of symptom relief is attained. It is important to note that the titration process may require a period of eight weeks or more to reach the optimal dose. The therapeutic regimen is maintained for the duration of the symptoms. The discontinuation of PEG is indicated in the event of the emergence of intolerable symptoms, including but not limited to: abdominal distension, cramps, and nausea. This decision is further supported by the absence of therapeutic benefit, as evidenced by the failure to alleviate constipation, despite the administration of the maximum tolerated dose[94].

b. **Guanylate cyclase agonists:** It is a good option for patients who do not get adequate symptom relief with PEG. These medicines help with abdominal pain and constipation in IBS-C and are usually well tolerated and used once daily[94].

   Linaclotide is probable that this is the most efficacious secretagogue currently available for IBS with constipation, although diarrhea is a common side effect[72]. The recommended daily dosage of this medication is 290 micrograms, administered in an empty stomach. In the event of the onset of diarrhea, the dosage is to be reduced to 72 or 145 micrograms per day. The discontinuation of linaclotide is indicated for patients whose symptoms do not demonstrate improvement following a four-week trial period[95].

   Plecanatide is an alternative guanylate cyclase agonist that exhibits a comparable mechanism of action. The recommended dosage of plecanatide is 3 milligrams once daily, with the option of ingestion with or without food. In the event of diarrhea, it is recommended to administer a daily dose to enhance tolerability. The administration of plekanatide is discontinued in patients exhibiting no response after a period of four weeks[96-98].

   The selection of linaclotide or plecanatide is predominantly influenced by factors such as accessibility and economic considerations, as the efficacy of these agents is comparable[96].

c. **Lubiprostone:** Lubiprostone, a chloride channel activator, is an effective drug for IBS with constipation. It is used as an alternative option for patients who experience side effects or do not improve with PEG and guanylate cyclase agonists, as it has fewer side effects of diarrhea. However, patients should be warned that nausea is a common side effect[72].

Lubiprostone is a chloride-2 channel activator that increases secretion of chloride-rich intestinal fluid and enhances peristalsis[99].

The approved dose of lubiprostone for IBS-C is 8 micrograms twice daily. Lubiprostone should be discontinued in patients who do not respond to a four-week trial. Patients who show some improvement after the first trial and have no tolerability problems may be titrated up to 24 mcg twice daily[100].

d. Tenapanor: Tenapanor is used in patients who have not responded to other treatments for IBS-C. Because it is a new agent, availability and cost may limit its use. Mechanism of Action - Tenapanor is a sodium/hydrogen exchanger 3 inhibitor. It acts locally in the small intestine and colon to reduce sodium and phosphate absorption, increase water retention, and promote bowel transit. Studies also show that it increases mucosal permeability and reduces visceral hypersensitivity[101,102]. The recommended dose is 50 micrograms twice daily. Improvement may be seen within a few days. Tenapanor should be discontinued in patients who do not respond to a four-week trial[15]. Reported adverse reactions include diarrhea, nausea, flatulence, and gas. Diarrhea is usually mild to moderate in severity and may improve with continued use of the drug[94].

ii. <u>IBS-D Treatment:</u>

a. Loperamide: Loperamide is a synthetic, peripheral opioid receptor agonist. It reduces the severity of diarrhea by inhibiting peristalsis, prolonging intestinal transit time, increasing intestinal water absorption, and decreasing stool volume. Loperamide also reduces symptoms of urgency by increasing resting anal sphincter tone[103]. Thus, loperamide may be an effective treatment for diarrhea in IBS. The initial dose is 2 mg, taken 45 minutes before each meal. The dose is adjusted according to the patient's response, with a maximum daily dose of 16 mg. It can also be administered prophylactically if the conditions that trigger symptoms are identified (e.g., exercise or stress). Side effects include abdominal pain, bloating, nausea, and constipation. Careful titration of the dose may prevent these side effects[72].

b. **Bile acid sequestrants:** Bile acid sequestrants (e.g., cholestyramine, colestipol, colesevelam) are employed to treat persistent diarrhea despite loperamide[94].

The drugs demonstrate comparable efficacy. The selection is contingent upon factors such as availability, cost, and patient preference regarding formulation (e.g., pill formulation or powder). In the event that the patient has a gallbladder, it is advisable for them to ingest bile acid sequestrants concurrently with their meals. In the absence of a gallbladder, it is

imperative that patients adhere to a regimen in which they administer the medication at least two hours apart from other medications. In the absence of a response to a two-week treatment period, the administration of an alternative sequestrant is permissible, or the treatment may be terminated[94]. Gastrointestinal adverse effects, including but not limited to bloating, flatulence, abdominal discomfort, and constipation, have been observed to impose limitations on the utilization of the aforementioned pharmaceutical agents[104].

c. Antibiotics and Probiotics: Given the possible microflora changes in IBS, it is possible that patients with diarrhea-predominant IBS may benefit from probiotics that affect the composition and metabolism of the microflora[31]. Rifaximin is a non-absorbable antibiotic and an effective drug for IBS-D in secondary care. However, its effect on abdominal pain is small. The drug is licensed in the US and some other countries for IBS with diarrhea[72].

d. **Histamine Receptör Antagonists:** In instances where patients demonstrate an absence of response to loperamide and at least one bile acid sequestrant, the administration of alosetron can be considered.

The recommended initial dosage of Alosetron is 0.5 milligrams administered once daily. In the event that the pharmaceutical agent is adequately tolerated, it is possible to increase the dosage to 0.5 milligrams twice daily after a period of four weeks in the patient whose irritable bowel syndrome with diarrhea (IBS-D) symptoms have not improved, with a maximum dosage of 1 milligram twice daily.

Given the risks associated with severe constipation and ischemic colitis, it is imperative to exclude gastrointestinal tract abnormalities, including but not limited to a history of mechanical obstruction, stricture, diverticulitis, and severe constipation, prior to the administration of treatment.

The administration of Aloestron is contraindicated in patients with a medical history marked by gastrointestinal tract abnormalities. It is imperative that the discontinuation of Alosetron be considered in patients who develop constipation. Non-severe constipation can be managed by restarting at a reduced dose[94].

Ondansetron has been investigated as a possible alternative 5-HT3 antagonist with a lower risk of ischemic colitis. Nevertheless, while ondansetron demonstrated efficacy in enhancing stool consistency, frequency, and urgency, it was observed to have no impact on abdominal discomfort. Preference for the use of alosetron in the treatment of IBS-D remains consistent[105].

e. **Eluxadoline:** Eluxadoline, a mixed opioid receptor antagonist, has been identified as an effective second-line treatment for IBS-D. Contraindicated in patients with sphincter of Oddi problems or a history of cholecystectomy, alcohol dependence, pancreatitis, or severe hepatic impairment. Due to the high number of reported side effects, this agent is considered a last-stage option for the treatment of refractory severe cases of IBS-D[72].

The standard dosage is 100 milligrams administered twice daily. In the event that adverse effects manifest as nausea or constipation, the dosage may be reduced to 75 milligrams administered twice daily. In patients who demonstrate an inadequate response to a 12-week trial, eluxadoline should be discontinued. A systematic evaluation of symptoms is conducted on a regular basis throughout the treatment period. Discontinuation of the pharmaceutical agent is recommended if the symptoms subside entirely within 12 months or beyond[94].

iii. **Medical Treatment for Global Symptoms:** The global prevalence of IBS is characterized by a constellation of symptoms, including abdominal pain, cramping, and bloating. In patients whose global symptoms have not improved despite lifestyle and dietary modifications and subtype-specific treatment, short-term or continuous pharmacotherapy options may be considered to control symptom exacerbations[94].

a. Antispasmodics: Some antispasmodics may be an effective treatment for general symptoms and abdominal pain in IBS. In a meta-analysis of 29 studies, antispasmodics were associated with significant improvements in abdominal pain, global assessment, and symptom scores compared with placebo[106]. Dry mouth, blurred vision, and dizziness are common side effects of antispasmodics[72].

b. Anticholinergics: We use anticholinergics for "as needed" treatment of acute pain attacks. The American College of Gastroenterology does not recommend their use for global symptoms of IBS[104]. If necessary, the recommended dosage of hyoscyamine is 0.125 to 0.25 milligrams, administered either orally or sublingually, at intervals of three to four times per day. The sublingual formulation has the potential to serve as a reassuring option for patients experiencing anxiety related to their symptoms.

Constipation is a prevalent adverse effect of anticholinergics, which may offer an added benefit in patients with IBS and diarrhea. In patients diagnosed with constipation, the administration of anticholinergics necessitates meticulous supervision. Alverine, mebeverine, otilonium bromide, pargeverine, trimebutine are other antispasmodic agents used in the treatment of IBS[94].

c. Tricyclic antidepressants: Tricyclic antidepressants, used as gut-brain neuromodulators, are an effective option for symptoms in IBS. In the treatment of IBS, TCAs act as pain modulator. They may also slow intestinal transit time, which may be beneficial in diarrhea-predominant IBS[107]. They should be used with caution and under close supervision in patients with constipation[108]. They should be started at a low dose (e.g. amitriptyline 10 mg once daily) and slowly increased to a maximum of 30-50 mg once daily[72].

Because of the delayed onset of action, treatment should be continued for three to four weeks before increasing the dose. If the patient is intolerant to a TCA, another TCA may be tried. TCAs may be combined with antispasmodics in patients with both episodic and persistent symptoms[94].

iv. <u>Brain-gut therapies:</u> Brain-gut therapies may be preferred for patients with symptom-focused mood disorders who do not want to receive pharmacological treatment and have resistant symptoms[94]. Psychological therapies should be considered when symptoms do not improve after 12 months of drug therapy[72].

a. Cognitive Behavioral Therapy: Cognitive Behavioral Therapy reduces pain, stress, depression, and anxiety in patients with IBS and may improve the severity and frequency of IBS symptoms[109].

b. **Gut-guided hypnotherapy:** Gut-guided hypnotherapy is used to encourage relaxation through suggestions, calm the digestive system and prevent unnecessary focus on symptoms. The aim of the sessions is to develop the perception that patients have complete control over their minds and bodies[94].

c. **Mindfulness-based stress reduction (MBSR):** MBSR is a mind-body relaxation technique designed to improve a person's ability to relax, cope with stress, and manage pain[94].

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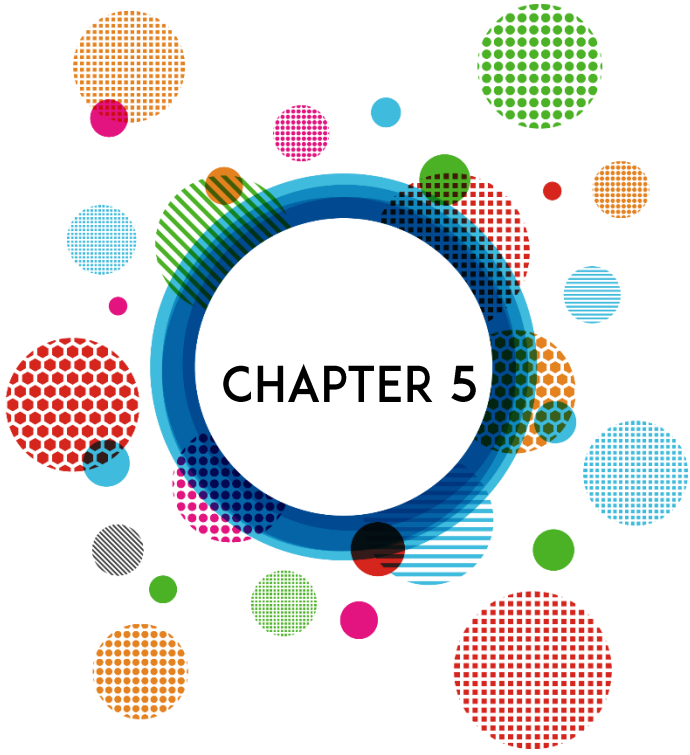

Medical and Veterinary Importance of Tick Infestation

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Significance of the Disease

Ticks are important ectoparasites that feed by sucking blood and play a role in the transmission of various pathogens for human and animal health. These parasites, which are distributed in almost every continent except the poles, constitute the second most risky ectoparasite group after mosquitoes in terms of public health due to their vectoring capacity. Ticks, which have been known since ancient times, cause various health problems in humans and animals both directly (blood sucking, toxic effect, allergic reaction, paralysis) and indirectly (pathogen, virus, bacteria, parasite). Throughout the world, including Türkiye, especially in regions where tick populations are dense, infestations adversely affect animal health, leading to yield losses and serious economic losses. These parasites can transmit the disease agents they carry to humans and animals through both mechanical and biological vectoring (Karaer et al., 1997; Orkun, 2022; Afşar et al., 2025).

Epidemiology of the disease

Ticks are distributed in various geographical regions of the world, especially in tropical and subtropical climate zones. Global climate changes have brought new risks to public health in recent years. Increasing temperature averages and climatic fluctuations change the ecological distribution of tick species, causing them to appear in areas where they have not been seen before. With this change, an increase in the number of cases due to tick bites has been observed. The main factors affecting the geographical distribution of ticks include vegetation, altitude, host animal populations and migratory birds. Especially migratory birds play an important role in the transport of ticks to remote areas. In Türkiye, cases of Crimean-Congo Haemorrhagic Fever (CCHF) transmitted by *Hyalomma* species ticks are frequently reported in spring and summer. Likewise, Marseille fever has been attracting attention with increasing number of cases in the Mediterranean region and Türkiye is also located in this region. In addition, Lyme disease, which was reported in 1990 as a vector of ticks, maintains its importance on a global scale. In order to develop effective control strategies against ticks, comprehensive studies on the ecological and epidemiological characteristics of these ectoparasites are needed (Unat, 1995; Bakırcı et al., 2012; Kim and Park,2023).

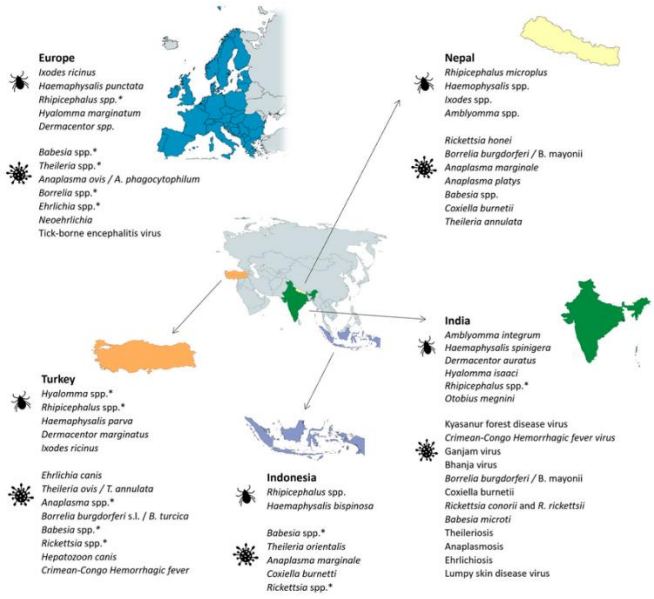

Figure 1. Most prevalent tick species and tick-borne pathogens in Eurasia (Europe, Türkiye, India, Nepal, Indonesia) (Fuante et al.,2023).

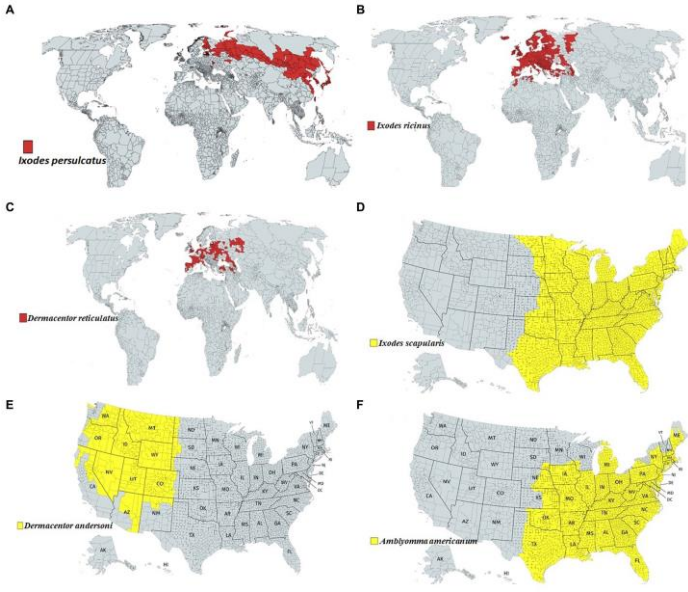

Figure 2. Approximate global distribution of some medically important ticks. (A) *Ixodes persulcatus* distribution in north-eastern Europe, some parts of Russia, China, Korea etc. (B) *Ixodes ricinus* in some parts of Europe and northern Africa. (C) *Dermacentor reticulatus* in some parts of Europe. (D) *Ixodes scapularis*, (E) *Dermacentor andersoni* and (F) *Amblyomma americanum* in Northern America (Shah ve ark., 2023)

Biology of Ticks

Ticks go through four stages of development in their life cycle: egg, larva, nymph and adult. Ticks belonging to the family *Ixodidae* are classified as 'hard ticks' and those belonging to the family *Argasidae* as 'soft ticks'. Depending on the species, the duration of blood sucking varies. The hatching larva feeds on more than one host until it reaches the adult form and changes shirts at each developmental stage. Female ticks die after oviposition and males die after mating. Ticks can transfer pathogens from an infected host to new hosts in subsequent developmental stages. This biological process is called transstadial transmission. In addition, some tick species can transmit disease agents to the next generation by passing them on in their eggs; this is called transovarial transmission. The high oviposition capacity of ticks allows pathogens to spread rapidly within the population and increase intergenerational transmission (Çiçek, 2009; Aydın and Coşkun 2019).

Tick-Borne Diseases

Ticks belonging to the *Ixodidae* family are of great importance in both medical and veterinary medicine due to the large number of pathogens they carry. These ticks have the capacity to carry disease agents both as vectors and reservoirs. The importance of tick-borne diseases on a global scale is increasing and scientific studies in this field continue to intensify. Crimean Congo Haemorrhagic Fever (CCHF), which has gained public health importance in recent years, is transmitted by some *Hyalomma* species, especially *Hyalomma marginatum*. This disease is associated with viruses of the genus *Nairovirus* of the *Bunyaviridae* family and may be characterised by hepatitis, severe bleeding disorders and high mortality rates. CCHF is endemic in many geographies, particularly in Africa, Asia, Eastern Europe and the Middle East. Infection can be transmitted by direct contact with blood, tissue and other bodily fluids of infected individuals, as well as by tick bites. Ticks also play an important role in the transmission of many zoonotic and animal disease agents such as tick-borne typhus, *Coxiella burnetii*, *plague*, *brucellosis*, *babesiosis*, *theileriosis*, *ehrlichiosis* and anaplasmosis. It is reported that approximately 80% of cattle worldwide are infected with ticks and these animals can be infected with different pathogens. The relationship of ticks with their wildlife hosts is critical in the biological cycle of tick-borne pathogens. Therefore, ecological and epidemiological studies are of great importance for the identification of tick-borne diseases and understanding the transmission cycle (Shah et al., 2023).

Host-Parasite Relationship

Species belonging to the families *Ixodidae* (hard ticks) and *Argasidae* (soft ticks) associate with a wide range of hosts, sucking blood from mammals, birds and reptiles. The majority of tick species do not show host specificity and require haematophagous feeding at all developmental stages (larvae, nymphs and adults).

While hard ticks usually leave the host after a single, prolonged period of bloodsucking, nymphal and adult stages of soft ticks show short-term but repetitive blood-sucking behaviour from one or more hosts. Mating in ticks usually occurs during bloodsucking; however, in ticks of the genus Ixodes, mating occurs before bloodsucking. Reproduction is mostly sexual, although some *Ixodidae* species also reproduce by parthenogenesis (Karaer et al., 1997; Troughton and Levin, 2007).

Clinic

Ticks pierce the skin of the host through their chelicerae, insert their hypostomes into the tissue and begin to suck blood in this way. During blood sucking, they can transmit some pathogenic microorganisms to the host. The saliva of the tick contains anticoagulant substances that inhibit blood clotting, which can lead to anaemia and even death in small animals, especially in heavy infestations. Local inflammatory reactions are usually observed at the site of the tick bite, including oedema, erythema, hyperaemia and pruritus. In addition, general symptoms such as burning sensation, tachypnoea, diarrhoea, nausea and tachycardia with systemic spread may occur. Especially in animals infected with Ixodes species ticks, anaemia is common and dermatological lesions and secondary infections are also likely to develop at the bite site.

Tick Paralysis

If ticks attach to body parts close to the central nervous system, tick paralysis, a rare but serious condition, can develop. This condition causes rapidly progressive paralysis, usually starting with pain in the legs, chest, arms and throat. Life-threatening symptoms such as dysphagia (difficulty swallowing) and dyspnoea (difficulty breathing) may occur due to paralysis. Clinical symptoms usually develop within 1 to 5 days after tick attachment and may result in death in some cases if not intervened (Belding, 1965; Deng et al., 2024).

Pathogenicity

Although ticks mostly cause infestation in wild animals, according to researches, tick infestation is also found in approximately 10% of domestic animals. While some tick species passively wait for their hosts to approach, others actively search for hosts. In the literature, 43 species belonging to the *Ixodidae* family have been reported to cause tick paralysis. This is caused by the release of neurotoxic compounds from the salivary glands of female ticks into the host. Depending on the severity of the toxic effect, in some cases paralysis can progress and lead to asphyxia, resulting in death. It is important that body integrity is not disturbed during tick removal. Appropriate tools such as clamps or blunt-tipped, toothless pliers should be used for this procedure. After removing the tick, the bite site should be cleaned with an antiseptic solution. If the extracted tick is to be destroyed, it should be kept in a

tube filled with alcohol; if pathogen examination is to be performed, it should be sent to the laboratory in a sterile tube (İnci and Düzlü., 2009; Eisen and Paddock., 2021).

Prevention of tick-borne diseases

In order to prevent tick-borne diseases, there is a need for comprehensive scientific research covering ecological, epidemiological and control strategies for ticks. Individual protection measures include wearing light-coloured clothing, tucking trouser legs into socks and treating clothing with insecticides (e.g. permethrin) or repellents in forested or scrubby areas. In addition, the body and clothes should be carefully checked for the presence of ticks when returning from the outdoor environment. Informing the public about ticks and tick-borne diseases by experts is an important step in reducing the risk of disease. It is important for individuals engaged in animal husbandry to apply antiparasitic drugs to their animals at regular intervals in order to control the tick population. Individuals working in meat-dairy enterprises and butchering in endemic regions should use personal protective equipment (gloves, goggles, etc.). In addition, basic protective equipment such as gloves, masks, aprons and goggles should be worn to prevent contact with blood, secretions or body fluids of infected humans and animals. In the fight against ticks belonging to the *Ixodidae* family, species-based ecological and epidemiological studies should be carried out taking into account regional seasonal distributions and appropriate acaricide applications should be made. Care should be taken to ensure that the chemicals used in this process are not harmful to human health. On the other hand, medication may not always be effective against ticks in the *Argasidae* family; therefore, physical improvement of animal shelters (e.g. plastering cracks in shelter walls) may be a more effective control strategy (Daltroy ve ark 2007; Iwasaki ve ark 2007; Eisen, 2022;Şahin ve Uslu, 2024).

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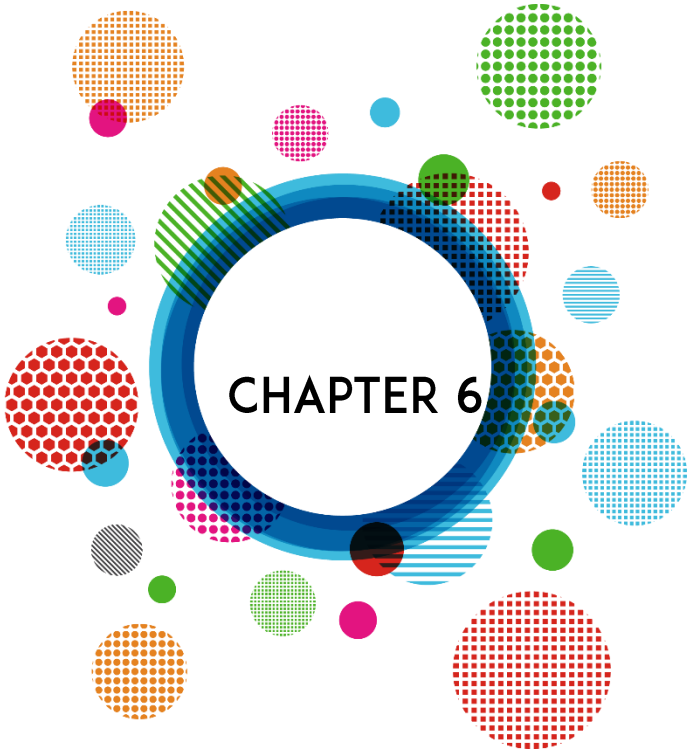

Bacterial Infections Transmitted Through Material in Animals

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1. INTRODUCTION

Bacterial infections transmitted through mating cause significant reproductive disorders in many domestic animal species and negatively affect both animal health and breeding activities. These infections are usually spread through asymptomatic carrier animals, reduce fertility rates and carry zoonotic risks (Quinn et al., 2011; Acha and Szyfres, 2003).This book chapter introduces the main bacterial infections seen in sheep, goats, cattle, horses, dogs and pigs, detailing their transmission routes, clinical symptoms, diagnostic methods and prevention and control strategies.

2. BACTERIAL INFECTIONS TRANSMITTED BY MOTION IN SHEEP AND GOATS

2.1. Campylobacteriosis

Campylobacteriosis is a bacterial infection caused by Campylobacter species, especially Campylobacter fetus subspecies. In ruminants, especially sheep and goats, this disease usually manifests itself with symptoms such as abortion, infertility and deterioration in reproductive performance. Mating is an important route of infection transmission and can cause economic losses in animal husbandry in this respect (Seyrek, 2015; Quinn et al., 2011).

2.1.1. Agent and Biology

Campylobacter spp. are Gram-negative, spiral-shaped, motile and microaerophilic bacteria. Especially Campylobacter fetus subsp. fetus and Campylobacter fetus subsp. venerealis cause disease in sheep and goats (Quinn et al., 2011). These bacteria show tropism to the reproductive system and can cause infection in the uterus, placenta and fetus tissues.

2.1.2. Transmission Routes

Campylobacteriosis is transmitted in sheep and goats mainly during coitus (mating). Infected male animals (especially bucks) can be carriers of the bacteria and can transmit the bacteria to females without semen. Transmission is also possible through contaminated feed, water or equipment, but sexual transmission is the most important factor in the spread of the disease in a herd (Acha & Szyfres, 2003).

2.1.3. Clinical Signs

The main signs that can be seen in sheep and goats with Campylobacteriosis are:

- Abortions in the second half of pregnancy
- Stillbirths or weak calves
- Low birth rate
- Early embryonic death

• Prolongation of the service period and re-estrus

Typically, necrotic liver lesions can be observed in aborted fetuses (Seyrek, 2015).

2.1.4. Diagnosis

Diagnosis is made by clinical signs, pattern of abortions and laboratory analysis. For the isolation and identification of Campylobacter spp., culture is usually performed from the stomach content, placenta and vaginal discharge samples of the aborted fetus. Molecular methods (PCR) are quite useful for rapid and specific diagnosis (Van Bergen et al., 2005).

2.1.5. Prevention and Control

The following strategies are recommended for the control of Campylobacteriosis:

• Separation of infected males from the herd

• Provision of hygienic mating conditions

• Vaccination (Campylobacter fetus vaccines are available in some countries)

• Antibiotic treatment should be used with caution and under veterinary supervision

• Isolation and appropriate removal of aborting animals (Humphrey et al., 2007)

2.1.6. Zoonotic Potential

Campylobacter spp. can also cause gastroenteritis in humans. Campylobacter jejuni in particular causes widespread infections in humans, while C. fetus can cause rare but serious systemic infections (e.g. sepsis, meningitis) in humans. Therefore, it is of great importance for those engaged in animal husbandry to pay attention to hygiene rules (Acha & Szyfres, 2003).

2.3. Chlamydiosis (Enzootic Abortion)

Chlamydiosis is a contagious and zoonotic disease caused by the Chlamydia abortus bacterium, which is especially common in sheep and goats. It causes reproductive disorders such as abortion in the last period of pregnancy, stillbirth and weak offspring. The spread of the agent to the environment through genital secretions by carrier animals leads to rapid transmission of the disease within the herd (Acha & Szyfres, 2003).

2.3.1. Agent and Biology

Chlamydia abortus is an obligate intracellular bacterium and is difficult to see with Gram staining. It usually settles in uterine epithelial cells and multiplies there, causing necrosis and inflammation. The agent is particularly concentrated on the

placenta and fetal membranes and spreads to the environment with abortion (Quinn et al., 2011).

2.3.2. Transmission Routes

• Vaginal discharges of aborting animals and contact with placental material

• Oral and nasal transmission (contaminated bedding, feed and water)

• Sexual transmission from infected rams to females

• Licking of fetal membranes or inhalation from contaminated environment

2.3.3. Clinical Signs

• Sudden abortion in the last third of pregnancy

• Birth of weak, lifeless offspring

• Retained placenta

• After abortion, female animals usually do not show any signs of systemic disease

• High rate of intra-herd spread

• Male animals usually do not show any signs

2.3.4. Diagnosis

Diagnosis is made by PCR, ELISA and cell culture of placenta, vaginal discharge and fetal membrane samples taken from animals that have aborted. Serological tests (complement fixation test, microimmunofluorescence) are used in herd-based screenings. In the placenta that emerges after abortion, a "thin membranous" structure and necrotic chorionic areas can typically be observed (Longbottom & Coulter, 2003).

2.3.5. Prevention and Control

• Isolation of abortive animals and disinfection of the environment

• Disposal of contaminated material by burning

• Use of vaccines (especially killed vaccines – live attenuated vaccines are also available in some countries)

• Application of antibiotics during risk periods (e.g. oxytetracycline)

• Pre-pregnancy serological screening

2.3.6. Zoonotic Potential

Chlamydia abortus is a zoonotic agent that can cause serious infections, especially in pregnant women, and can cause miscarriage, premature birth and

septicemic infections. Therefore, contact of pregnant women with sheep and goats that give birth should be prevented (Wheelhouse & Longbottom, 2012).

3. BACTERIAL INFECTIONS TRANSMITTED BY MOTION IN CATTLE

3.1. Bovine Genital Campylobacteriosis

Bovine Genital Campylobacteriosis (BGC) is an important sexually transmitted disease that causes infection in the genital system of cattle. The agent is usually Campylobacter fetus subsp. venerealis, and causes problems such as fertility loss, late pregnancy and miscarriage in female animals (Quinn et al., 2011).

3.1.1. Agent and Biology

C. fetus subsp. venerealis is a microaerophilic, spiral-structured and motile Gram-negative bacterium. It settles in the vagina and uterine mucosa in female animals and prevents fertilization, while it can remain as a carrier in the prepuce and glans penis mucosa in bulls (Acha & Szyfres, 2003).

3.1.2. Transmission Routes

Transmission occurs mainly through transmission from infected bulls to healthy females during natural mating. Transmission has also been reported through artificial insemination. Bulls are mostly asymptomatic carriers (Corbeil, 2007).

3.1.3. Clinical Signs

- Early embryonic death
- Prolongation of the service period
- Irregular estrus
- Decrease in pregnancy rates

No clinical signs are observed in bulls; however, they play an important role in the spread of the disease (Seyrek, 2015).

3.1.4. Diagnosis

Diagnosis can be made by culturing vaginal mucus samples or bull prepuce fluid. Molecular diagnostic methods such as PCR provide highly accurate results (Van Bergen et al., 2005).

3.1.5. Prevention and Control

• Regular screening of bulls

• Removal of infected bulls from breeding

• Transition to artificial insemination

• Vaccination (available in some countries)

3.2. Situations Confused with Tritrichomoniasis

Tritrichomoniasis is a sexually transmitted disease caused by the protozoan Tritrichomonas foetus and can cause similar clinical findings to Bovine Genital Campylobacteriosis. Fertility problems, late pregnancy and early embryo death are prominent in both diseases (BonDurant, 2005).

3.2.1. Clinical Approach in Terms of Differential Diagnosis

• Both diseases are asymptomatic in bulls.

• Abortion rates are high in females.

• Differential diagnosis should be made with laboratory tests (culture, PCR).

• While the agent of tritrichomoniasis can be quickly diagnosed by microscopy, special culture conditions are required for Campylobacter (Quinn et al., 2011).

3.2.2. Prevention Approaches

• Similar control measures are taken (bull screening, artificial insemination, removal of infected animals from the herd).

• It should be taken into account that the infection can spread rapidly, especially in collective farms.

3.3. Brucellosis (Brucella abortus)

Brucellosis is a serious zoonotic infection caused mostly by Brucella abortus in cattle and can be transmitted through mating and environmental routes. It is characterized by abortion, postpartum complications and infertility in female animals (Godfroid et al., 2011).

3.3.1. Agent and Biology

Brucella abortus settles in the genital organs of cattle and causes infection in the placenta. It causes abortions especially in the second half of pregnancy. The bacteria

are shed in large amounts during birth and contaminate the environment (Corbel, 2006).

3.3.2. Transmission Routes

Transmission usually occurs through contact with infected materials (placenta, fetus, vaginal discharge). However, transmission from bull to female is also possible during mating (Quinn et al., 2011).

3.3.3. Clinical Signs

• Abortion (especially between 5-7 months)

• Retentio secundae

• Metritis and endometritis

• Orchitis and epididymitis in males

Some animals can shed bacteria with milk or genital secretions for a long time (Seyrek, 2015).

3.3.4. Diagnosis

Diagnosis is made with serological tests (Rose-Bengal, SAT, ELISA) and culture methods. Molecular techniques give faster results. Abortion materials are valuable samples in diagnosis (Godfroid et al., 2011).

3.3.5. Prevention and Control

• Removal of Brucella positive animals from the herd

• Application of S19 or RB51 vaccines to young females

• Consumption of pasteurized milk

• Provision of hygienic birth environments

It also carries a serious risk for humans due to its zoonotic nature.

4. BACTERIAL INFECTIONS TRANSMITTED BY MEATBREEDING IN HORSES

4.1. Taylorella equigenitalis

Contagious Equine Metritis (CEM) is a highly contagious bacterial reproductive system infection transmitted by mating in horses. The agent is Taylorella equigenitalis, which causes fertility disorders and temporary infertility, especially in female horses (Timoney, 1996).

4.1.1. Agent and Biology

T. equigenitalis is a non-motile, Gram-negative, coccobacillus, microaerophilic bacterium. It infects the uterus and vagina of female horses, while it usually remains asymptomatic and remains a carrier in stallions (Quinn et al., 2011).

4.1.2. Transmission Routes

The bacteria is directly transmitted during mating. It can also spread via contaminated semen during artificial insemination. Contaminated equipment may also play a role in transmission (Foote, 2001).

4.1.3. Clinical Signs

• Vaginal discharge (a few days after mating)

• Transient infertility

• Endometritis

• Generally asymptomatic in men

4.1.4. Diagnosis

Diagnosis is made by culture or PCR method with samples taken from vaginal and cervical swabs or prepuce. The disease is among the diseases that must be reported in many countries (Timoney, 1996).

4.1.5. Prevention and Control

• Isolation and treatment of infected stallions

• Testing practices before artificial insemination

• Mandatory testing in international transports

• Hygienic mating practices

4.2. Klebsiella pneumoniae and Pseudomonas aeruginosa

Klebsiella pneumoniae and Pseudomonas aeruginosa are other important bacterial agents that can cause genital tract infections in horses and can be transmitted through mating. These pathogens can remain as carriers, especially in stallions, and can be transmitted to females during artificial insemination or natural mating (Causey, 2006).

4.2.1. Causal Characteristics

Klebsiella pneumoniae is a capsulated, facultative anaerobe, Gram-negative rod-shaped bacteria.

Pseudomonas aeruginosa is an aerobic, motile, Gram-negative rod-shaped bacterium. Both agents can be of environmental origin and affect reproduction by colonizing the genital area (Quinn et al., 2011).

4.2.2. Transmission Routes

• Natural mating

• Use of contaminated semen

• Unhygienic artificial insemination equipment

• Colonization on the prepuce or penis surface in stallions

4.2.3. Clinical Signs

• Decreased fertility in females

• Slight vaginal discharge

• Endometritis

• Inability to conceive

• Clinical signs are usually absent in males, but carriage is possible

4.2.4. Diagnosis

It can be isolated from the prepuce swabs of the stallion or the uterine fluid of the female horse by culture. Antibiotic sensitivity tests are guiding for treatment (Causey, 2006).

4.2.5. Prevention and Control

• Regular bacteriological screenings

• Sperm control before artificial insemination

• Genital examination of stallions before the breeding season

Local antibacterial treatment applications when necessary.

5. BACTERIAL INFECTIONS TRANSMITTED BY MOTION IN DOGS

5.1. Brucella canis Infection

Brucella canis is an important bacterial agent that can be transmitted through mating in dogs and causes reproductive disorders in both female and male individuals. This zoonotic bacterium can lso cause infection in humans (Lucero et al., 2005).

5.1.1. Agent and Biology

B. canis is a Gram-negative, aerobic, non-motile coccobacillus that is located intracellularly. It can cause long-term infections in the reproductive system, lymph nodes and spleen. Bacteremia usually persists for a long time in infected individuals (Carmichael, 1990).

5.1.2. Transmission Routes

• Natural mating

• Contact via sperm, vaginal discharge and urine

• Contact with abortion materials

• Transplacental transmission

• Respiratory transmission is also possible in laboratory or shelter environments

5.1.3. Clinical Signs

In bitches:

• Abortion in late pregnancy

• Vaginal discharge

• Recurrent abortions

• Temporary infertility

In bitches:

• Epididymitis, orchitis

• Testicular atrophy

• Painful ejaculation

• Decreased sperm quality

5.1.4. Diagnosis

Diagnosis is made with serological tests (RSAT, 2-ME RSAT, ELISA) and blood cultures. Molecular diagnostic methods (PCR) increase sensitivity. Attention should be paid to false positives in serological tests (Hollett, 2006).

5.1.5. Prevention and Control

• Avoiding mating infected individuals

• Pre-production serological screening

• Isolation or removal of infected individuals from production

• Human contact should be minimized against zoonotic risk

• No vaccine is available

5.2. Mycoplasma spp. and Ureaplasma spp. Infections

Mycoplasma spp. and Ureaplasma spp. are bacteria that can become pathogenic under certain conditions, although they can be found in the normal flora of the genital tract in dogs. These microorganisms can be transmitted through mating and can negatively affect fertility (Ball et al., 2008).

5.2.1. Agent and Characteristics

Mycoplasma and Ureaplasma are pleomorphic bacteria without a cell wall. They are difficult to culture and require special media. They are frequently isolated in reproductive system infections. In particular, Mycoplasma canis and Ureaplasma urealyticum are the most common strains (Quinn et al., 2011).

5.2.2. Transmission Routes

• Natural mating

• Artificial insemination material

• Transmission from infected mother to puppy during birth

• Direct contact with semen or vaginal discharge

5.2.3. Clinical Signs

In bitches:

• Recurrent abortions

• Vaginitis

• Endometritis

• Infertility

In bitches:

• Prostatitis

• Epididymitis

• Low sperm motility

• Azoospermia or oligospermia

5.2.4. Diagnosis

For diagnosis, cultures are taken from urogenital samples or PCR is used. Serological tests are of limited information. Mycoplasmas are generally resistant to beta-lactam antibiotics; therefore, sensitivity tests are important (Ball et al., 2008).

5.2.5. Prevention and Control

• Pre-production mycoplasma screening

• Controlled and sterile conditions for artificial insemination

• Removal of symptomatic individuals from production

• Long-term antibiotic treatments (e.g. doxycycline) may be required

• Improvement of hygiene conditions

6. BACTERIAL INFECTIONS TRANSMITTED BY MUTTING IN PIGS

6.1. Brucella suis Infection

Brucella suis is an important pathogen that affects reproductive health, can be transmitted through mating, and has zoonotic potential, especially in pigs. It can be subclinical in males and females, which makes diagnosis and control difficult (Acha & Szyfres, 2003).

6.1.1. Agent and Biology

B. suis is a Gram-negative, facultative intracellular coccobacillus. It is more virulent than other Brucella species and can survive in lymphoid organs for a long time. It consists of five biotypes, especially biotypes 1 and 3 are pathogenic in pigs (Alton et al., 1988).

6.1.2. Transmission Routes

• Direct mating

• Contact with infected vaginal discharge and semen

• Abortion materials and contaminated environment

• Inhalation or oral (secondary transmission)

6.1.3. Clinical Signs

In sows:

• Abortions (especially in late pregnancy)

• Postpartum infections

• Infertility

In boars:

• Epididymitis and orchitis

• Decreased libido

• Infertility

6.1.4. Diagnosis

Serological tests (Rose Bengal, ELISA, CFT) and culture methods are used for diagnosis. However, laboratory safety is important due to the zoonotic nature of B. suis. Molecular methods (PCR) provide rapid and sensitive results (FAO/OIE/WHO, 2006).

6.1.5. Prevention and Control

• Separation of infected animals from the herd

• Serological screening and isolation

• Safe farm hygiene

• No vaccine available

• Human contact should be minimized (especially laboratory workers)

6.2. Leptospira spp. Infections

Leptospira spp. is a spiral-shaped bacterium that can be transmitted through mating, is common in pigs, and has a high zoonotic risk. The infection is mostly chronic and can spread within the herd without being noticed (Levett, 2001).

6.2.1. Agent and Characteristics

Serovars belonging to the Leptospira interrogans complex, especially Pomona, Bratislava and Icterohaemorrhagiae, are infectious agents in pigs. They can survive in water or moist environments for long periods (Ellis, 2015).

6.2.2. Transmission Routes

• Contact with genital secretions during mating

• Transmission through urine (oral, mucosal or dermal)

• Placental transmission

• Contaminated water, feed or shelter

6.2.3. Clinical Signs

In sows:

• Abortion

• Weak birth of offspring

• Postpartum metritis

In boars:

• Subclinical course is common

• Rarely epididymitis

6.2.4. Diagnosis

Serological diagnostic methods (MAT, ELISA) are widely used. Culture from urine and blood samples is possible under special conditions. Rapid diagnosis is possible with PCR (OIE, 2021).

6.2.5. Prevention and Control

• Vaccination (especially in commercial flocks)

• Disinfection of water sources

• Rodent control

• Isolation of infected animals

• Hygienic mating environment

7. CONCLUSION

Bacterial infections transmitted through mating reduce the reproductive performance of animals, cause disease spread within the flock and also threaten human health due to their zoonotic potential. Pre-production screening tests, isolation of infected animals, hygienic mating conditions and strategies such as vaccination are important for the control of these infections. In addition, the role of veterinarians in the diagnosis and notification of diseases is critical for both animal welfare and public health.

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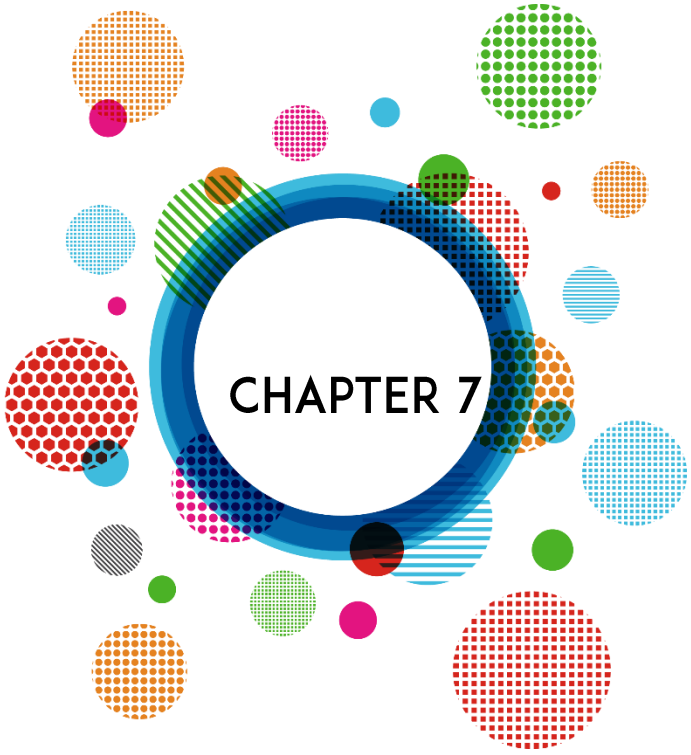

Spermatological Examination Methods in Rams

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INTRODUCTION

Spermatological examinations are performed to check whether an animal can be used as a breeder through reproductive organ examinations, to determine possible diseases or disorders and reproductive capacity (Chenoweth and Lorton 2014). Before focusing on spermatological parameters related to fertilization ability, it is necessary for the animal to undergo a number of examinations such as physical examination, libido and mating ability, examination of internal and external reproductive organs in order to determine its fertilization capacity (Hafez and Hafez 1993; İleri et al. 2000). There are many tests for the evaluation of ram sperm according to different criteria. We can classify these as macroscopic examinations, microscopic examinations and advanced techniques.

1. Macroscopic examinations

These are examinations performed visually without the need for a microscope or other device in the evaluation of semen. Volume, color, viscosity (consistency), and odor are types of examinations that can be examined macroscopically for ram semen. Since mass movement examination in ram semen can be seen with the naked eye without the need for a microscope, it has been included in macroscopic examinations by some researchers (İleri et al. 2000).

Volume

The volume, which is the amount of sperm obtained in an ejaculation, begins to be produced in male lambs from the age of 2-2.5 months and continues to increase after the animal is 18 months old until it is 4 years old. The volume of semen obtained from a healthy adult ram varies, but is around 0.5-2.0 ml, with an average of 1 ml. (Maxwell and Salamon 1993). The semen volume of rams generally varies depending on the season, age of the animal, care and nutrition, disease status, method of collection, frequency of collection, person collecting the semen, presence of females in the environment and performance of the ram (Evans and Maxwell 1987; Gökçen 1990). The volume of ram semen is low compared to the volume of many other farm animals. The ejaculate obtained is called aspermia when it does not contain sperm, hypospermia when it is lower than the required volume and hyperspermia when it is higher than the required volume (İleri et al. 2000).

Color

The color of a healthy ram's sperm can vary from light cream to dark cream depending on the decrease in density, depending on the density of the spermatozoon, the secretion of the accessory glands and the consistency of the sperm. (İleri et al. 2000; Sevinç 1977). Color changes other than these mentioned colors are evaluated as disease-related. If the sperm appears in a red-brown color, it is an indication that the ejaculate is contaminated with blood (hemospermia), if it appears in a yellow

color, it is contaminated with urine (urospermia) and if it appears in a yellow-greenish color, it is contaminated with pus (pyospermia). Other foreign substances seen in the sperm can be observed as sediment or particles (Sevinç 1977; Hafez and Hafez 1993; İleri et al. 2000).

Smell

Sperm has a unique odor. The presence of odors other than this odor is evaluated as a pathological condition (Sönmez 2013).

Viscosity (Consistency)

By definition, viscosity is called the resistance of liquids to flow. The consistency of sperm can be measured with a viscometer, and the consistency examination can be subjectively evaluated on a scale of 0-5 without using a viscometer (Mert et al. 2016). In other words, experienced researchers can have an idea about the sperm concentration in the sperm by subjectively evaluating the consistency (İleri et al. 2000).

A normal ram semen has a thick consistency due to its dense spermatozoon content (Çoyan et al 2002). Consistency is inversely proportional to fluidity and directly proportional to density. In semen with high viscosity, the progression speed of progressive motile spermatozoa is lower (Alçay 2015).

Mass Movement

Mass movement is generally defined as the collective fluctuating movements of spermatozoa. Ram ejaculates with high sperm concentration can be examined with the naked eye as well as with a microscope (Çoyan et al. 2002). The sperms taken into the sperm collection glass are slightly exposed to light and the presence of a wavy movement is observed. The ++++ scoring system (+, ++, +++, ++++) is used in the evaluation. +++ and ++++ are accepted as passing criteria. If there are intense circular movements and a boiling-like movement in the sperm, it can be said that the sperm density is high. There is a positive correlation between the degree of mass movement and the sperm density (Evans and Maxwell 1987; İleri et al. 2000).

2. Microscopic examinations

These tests, which have a special importance in the evaluation of sperm quality, are generally based on the evaluation of the vitality and morphology of spermatozoa through a microscope.

Mass Movement

Since mass movement can be seen with the eye in ejaculates containing dense spermatozoa such as rams, billy goats, and roosters, it has also been mentioned in macroscopic examinations, as some researchers have stated. By looking at the mass

movement of sperm, we can obtain information about its motility, density, and fertility, since there is an important relationship between them. For this reason, the importance of this examination plays a major role in some species such as rams and billy goats where mass movement is observed (İleri et al. 2000). Fresh and undiluted sperm sample is used in microscopic examination. A drop of the sample taken (5 µl) is dropped onto a slide that has been pre-warmed and is approximately 37 ºC and examined using a light microscope with a heating table or a phase contrast microscope using 100x magnification. The observed fluctuations, boiling or vortex-like movements in the droplet are scored by grading. Although the scoring method varies according to the researchers, there are those who use a scoring of 0-5 or 0-10 and those who use the ++++ evaluation system (Hafez and Hafez 1993, İleri et al 2000, Ak 2005b). Regardless of the system used to evaluate, information is obtained about sperm motility, density and potential fertility ability by mass movement examination of the sperm (Hafez 1993).

Density

Spermatozoon density refers to the number of spermatozoon in a unit volume (ml). Density determination in sperm can be done with different methods such as hemocytomeric method, photolometric method and electronic counter method. The density of native ram sperm is 2-3x109 /ml. Concentration determination in sperm is important for adjusting the extender dose to be used (Hafez 1993). The sperm density of rams generally varies depending on the season, age of the animal, care and nutrition, disease status, sperm collection method, frequency of sperm collection, person collecting the sperm, presence of females in the environment and performance of the ram (Evans and Maxwell 1987; Gökçen 1990). Again, due to the high seminal plasma volume of ram sperm collected using an electroejaculator, the sperm density per unit volume is low (MarcoJiménez et al. 2005). In general, the density of a sperm is determined using the hemocytometric method. For this purpose, special slides (Thoma, Neubauer, Petroff-Hauser, Improved Neubauer, Makler® chamber, Burker etc.) used in this field are the most preferred in practice. In order to determine the density of sperm, it is necessary to kill/prevent the movement of live spermatozoa. For this purpose, different buffer solutions (glutaraldehyde, formol sodium citrate, formol-saline etc.) are used at a ratio of 1/200. The sperms whose movements are stopped are mixed homogeneously and examined by counting the heads using a microscope with 100x-200x magnification. There are 25 large and 16 small squares in two separate counting areas on the slides used for counting (Thoma Slide consists of 16 large and 25 small squares). It is recommended to count at least 5 large squares in order for the counting process to yield healthy results. The number of spermatozoa present in mm3 volume is determined with the formula. The obtained number should be multiplied by $1x10^3$ to express the number of spermatozoa in ml (cm^3). The total number of spermatozoa in the ejaculate is calculated by multiplying

the result by the ejaculate volume (Hafez and Hafez 1993). With the developing technological processes today, the use of automatic devices such as colorimeters, photometers and spectrophotometers to determine sperm density has become widespread. Although these devices provide convenience and time savings, they require regular control and calibration at certain times. Compared to the hemocytometric method, these devices provide faster and more repeatable results. Sperm density can also be evaluated using flow cytometry devices. In these devices, sperm is evaluated individually with a liquid flow, without considering foreign substances and particles (Evenson et al. 1993). In addition, density determination is also possible today using computer-aided sperm analysis devices (CASA). This method provides faster results than previously used methods such as hemocytometry, and provides the opportunity to reach more objective data (Amann and Waberski 2014).

Motility

Spermatozoon movements are generally divided into four. These are defined as forward/progressive movement, circular movement, vibration/vibrator movement in place and backward/reverse movement (Hafez 1993). The ratio of spermatozoa moving forward and linearly in the direction of their heads to all spermatozoa is called motility, and spermatozoa with this ability are called motile spermatozoa.

The ability of sperm to advance in the female genital tract and reach the ampulla of the oviduct where fertilization takes place is of critical importance in the successful achievement of pregnancy, especially due to its successful passage through the cumulus cells and zona pellucida barrier on the surface of the oocyte (İleri et al, 2000; Sönmez 2013). The fact that only spermatozoa moving in a straight linear direction in the head direction can reach the fertilization area shows that motility examination is of great importance in determining potential fertility and that there is an important relationship between these two (Çoyan et al, 2002; Hafez and Hafez 1993; İleri et al 2000, Sönmez 2013).

In motility examination, dense ejaculates should be examined after being diluted several times. It is important that the diluent to be used has buffer properties and is at the same temperature as the sperm (such as sodium-citrate, isotonic sodium chloride) and that it is examined on a pre-heated slide. A small amount (3-5 µl) of sperm taken from the diluted sample is placed on the slide and covered with a coverslip. It is evaluated under a phase contrast microscope with a heating table and at 400 magnification. Although a subjective assessment is made, in order to maximize accuracy, the flow caused by vibration should stop after the coverslip is closed. At least 3 separate areas are examined and the percentage of spermatozoon with forward linear movement is calculated (İleri et al. 2000; Sönmez 2013). Spermatozoon motility is affected by many factors such as the content of the

extender, dilution method, ambient temperature, osmotic pressure, time, metabolite residues, Reactive Oxygen Species (ROS) and hygiene conditions (Hafez 1993).

Dead/Live Spermatozoon Ratio and Morphological Disorders

Each ejaculate contains a certain amount of spermatozoa that have lost their morphological integrity and/or vitality. However, it is expected that this ratio will not exceed 15-20% in a ram spermatozoon to be used as a breeder (Ak 2005b). In addition to phase contrast and light microscopy, electron microscopy can also be used for detailed morphological examination in determining the dead/live ratio or structural disorders. Vital dyes such as eosin-nigrosin, propidium iodide and carboxyfluorescein diacetate, which are related to cell membrane permeability, are used to distinguish dead spermatozoa. The most commonly used method for the detection of dead spermatozoa is the eosin-nigrosin staining method. Eosin, a vital dye, passes through the membrane of dead spermatozoa and stains the cytoplasm pink-red, whereas the cytoplasm of live spermatozoa is not stained because the cell membrane of eosin does not allow it to pass. Nigrosin is the background dye used to create negative contrast on the slide. The effects of these dyes, which give different reactions according to membrane integrity, vary depending on factors such as the amount of dye used, the temperature of the slide, the thickness of the sputum, the drying temperature, the structure of the sperm extender and the number of spermatozoa. In addition, differences in results can be seen between application methods and different operators (Nur et al. 2011). Although motile spermatozoa are considered live, membrane permeability may be impaired. Therefore, the rate of live spermatozoa in the ejaculate is important in supporting motility in the evaluation of fertility. The condition in which all spermatozoa in the ejaculate are dead is called "necrozoospermia". The expected live sperm ratio in a healthy ram ejaculate is at least 80%. It is stated that ejaculates containing a high percentage of dead spermatozoa are not suitable for insemination purposes because this may cause an increase in free oxygen radicals that disrupt the sperm membrane structure (Tekin 1994, Tümen et al. 1991).

Different classifications are used to determine morphological disorders. Some researchers have defined disorders occurring during spermatogenesis as primary disorders (pear-headed, narrow-headed, double-headed, abaxial, paraxial, retroaxial attachment, sharply curved, fibrillar tail, etc.), and disorders occurring during the passage of spermatozoa through the epididymal canal system as secondary disorders (tailless head, proximal and distal droplet, curled tail, etc.). In another evaluation, some researchers have classified the disorders as major and minor according to the degree of morphological disorders (Morrow 1986). In another classification method, disorders occurring during spermatogenesis are called primary, disorders occurring during the passage of the epididymal canal system are called secondary, and disorders occurring during or after ejaculation are called tertiary disorders (Hafez

1993). Today, in the classification of morphological disorders, the region where the disorder is located is generally taken into account. This classification is as follows: acrosome, head, implantation fossa, head-to-middle attachment, middle and tail (Ak 2005b). In all these different systems, various staining techniques such as rose bengal, India ink, giemsa, methylviolet, opal blue and fixation solutions such as Hancock Solution are used to determine the rate of morphological disorders (Ak 2005b).

3. Hypo-osmotic swelling test (HOST)

The hypo-osmotic swelling test is used to determine functional membrane integrity in spermatozoa. When spermatozoa are exposed to environments with low osmotic pressure, they exhibit membranous reactions aimed at regulating intracellular and surrounding osmotic pressures. The membrane structures of spermatozoa are semi-permeable and they swell by taking fluid into the cell in a hypo-osmotic environment. In particular, their head sections swell and their tails curl. This test is basically a test of whether the membrane integrity of a live spermatozoon is intact.

4. Advanced spermatological examination methods

Thanks to the changing and developing biotechnological devices over time, spermatological analysis methods that can provide more reliable and detailed results have begun to be used. The most well-known of these are the computer-aided sperm analysis device CASA (Computer Assisted Sperm Analysis) and the Flow cytometry device.

Computer-Aided Sperm Analysis Device (CASA)

Until the development of the CASA device by Dott and Foster in 1979 (Verstegen et al. 2002), the microscope was the classical method used to determine sperm quality. This method, which is widely used in the field and is considered the first motility analysis performed by eye, has disadvantages such as the subjective nature of the evaluation, the low number of analyzed cells, low repeatability, sperm movements being open to external factors and the need for a long time for analysis (Foote 2002).

CASA was first developed by Rothschild and then Elliott using a simple setup based on taking photographs of spermatozoa seen under the microscope at two-second intervals in order to objectively examine the spermatozoa. Motile and stationary spermatozoa were first determined with these photographs (Elliott et al. 1973). This procedure, called the “Elliot Photographic Procedure”, was modified and used by many researchers (Makler 1978, Revell and Wood 1978). In the following years, sperm movements were recorded for 15 seconds using analog cameras. It was

reported that they were examined separately by several people on television screens (Foote et al. 1978).

These systems, which are the basis of CASA, allowed the determination of real-time motility and kinematic values of spermatozoa with the development of computer systems (Katz et al. 1985). In general, the system content includes a computer unit, a camera setup and a phase contrast microscope with a heating table. Thanks to this system, in addition to sperm motility, kinematic movement parameters related to movement are also evaluated (Hafez and Hafez 1993).

There are slides (Leja etc.) designed in accordance with the system for CASA controls. It has been reported that varying findings can be obtained in different areas of the slides and that density data may differ if the slide wells are filled insufficiently (Douglas et al. 2005a; 2005b). Total motility (TM) in computer-aided analyses; It is the ratio of spermatozoa with motile ability to all spermatozoa. Progressive motility (PM) refers to the ratio of spermatozoa that move forward in the direction of their head to all spermatozoa. Nonprogressive motile spermatozoa refer to spermatozoa that have motile ability but are not strong, do not follow a linear path or move unusually, and immotile spermatozoa refer to spermatozoa that do not show any motile behavior at all (Verstegen et al. 2002; Foote 2002). The parameters analyzed in the CASA device may vary depending on factors such as whether the sperm is native or frozen-thawed, the features of the system used, the image frequency of the connected camera system, the type of slide preferred for analysis, the examination temperature, the calibration of the device parameters, whether the maintenance and controls of the device are done on time, and the expertise of the researcher performing the application. In particular, the type of slide used and the frequency of the camera (25, 50, 100, 200 Hz) are very important (Mortimer 2000; Verstegen et al 2002; Castellini et al. 2011). These systems have the ability to analyze morphometric analyses in a short time with high accuracy and repeatability.

The CASA device, total motility (%); progressive motility (%); the speed of the spermatozoon head during its movement on a 2-dimensional real curvilinear path, which are the spermatozoon kinematic velocity parameters (VCL) in μm/s; (VSL) shows the linear distance between two points of the spermatozoon head in μm/s; (VAP) shows the speed of the average distance covered by the spermatozoon head in μm/s. In addition, (STR) gives information about the path followed by the spermatozoon and the distance it has traveled, and it expresses the linearity of the average path (%), i.e. (VSL/VAP X 100); (LIN) shows the linearity of the curvilinear path (%), i.e. (VSL/VCL X 100) (Verstegen et al. 2002).

Flow Cytometry Device (Flowcytometer)

The flow cytometry method is basically based on the principle of marking a large number of spermatozoa directed to the capillary canal system of the device with

fluorescent dyes specific to the type of examination and evaluating them with high accuracy in a short time (Gillan et al. 2005).

Fluorescent-attached phase contrast microscope and flow cytometry are used in many spermatological analyses such as vitality, mitochondrial activity, capacitation, acrosome membrane, spermatozoon membrane, DNA fragmentation and oxidative stress. An important advantage of flow cytometry, which is used by every researcher working on sperm evaluation today as the greatest assistant in terms of time and accuracy, is its high level of experimental reproducibility. It is also a sensitive method for the detection of small nuances between spermatozoon populations that cannot be detected by other methods (Gillan et al. 2005). As is known, plasma membrane, acrosome membrane and mitochondria are among the most affected cell structures during cryopreservation in spermatozoa (Watson 2000). Again, plasma membrane and acrosome integrity (PMAI) and mitochondrial membrane potential (MMP) values of post-thaw spermatozoa are important criteria for successful fertilization. Physical and functional integrity damages in the membrane are an indicator of decreased fertilization ability of spermatozoa (Silva and Gadella 2006). Mitochondria, which are the energy source required for all cellular functions, are also of great importance for spermatozoon motility. In this case, damages in plasma or acrosome membranes can trigger premature acrosome reaction and cause significant decreases in fertility (Garner et al. 1997; Wassarman 1999).

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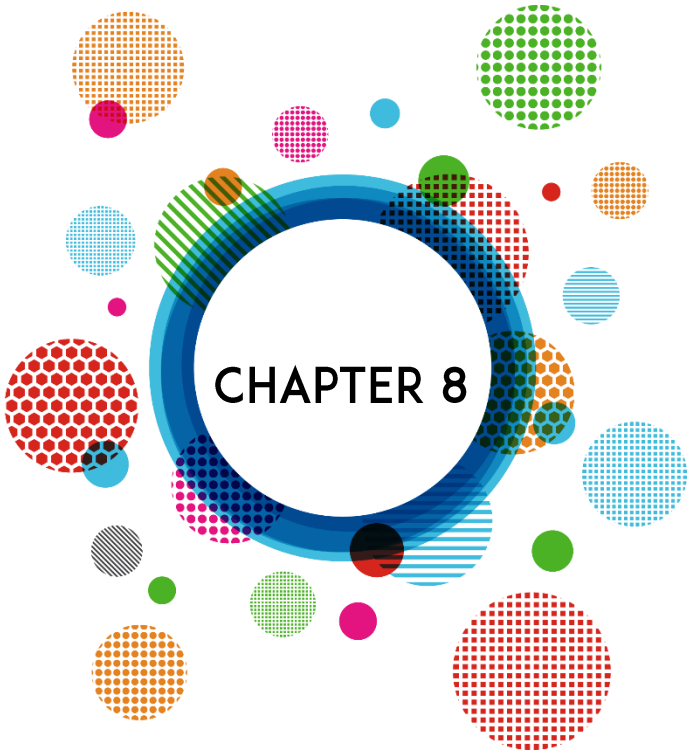

Fatal Home Accidents in Children

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Introduction

Home accidents that cause death are accidents such as falls, burns, poisoning, drowning and cuts that children are exposed to in the home environment (Simpson, Turnbull, Ardagh & Richardson, 2009). According to the World Health Organization (WHO), a significant proportion of deaths and injuries in childhood occur as a result of home accidents (Titi, van Niekerk & Ahmed, 2018). Such accidents constitute an important public health problem in developed and developing countries.

The prevalence of home accidents in children may vary according to age groups and the environment they live in. Especially children in the 0-5 age group are more prone to home accidents because of their developmental characteristics and curiosity (Titi, van Niekerk & Ahmed, 2018). Studies conducted in the United States of America show that approximately 3 million children present to the emergency department every year due to home accidents (Falesi, Berni & Strambi, 2008). A similar situation is also observed in Turkey; a significant proportion of admissions to pediatric emergency departments are due to home accidents (Villalba-Cota, Trujillo-Hernández, Vásquez, Coll-Cárdenas & Torres-Ornelas, 2004).

Findings

Home accidents occur as a result of a combination of many factors (Titi, van Niekerk & Ahmed, 2018). These factors vary depending on the age and developmental level of the child, the safety of the home environment and the level of parental supervision.

Table I: Accidents by Age and Developmental Level

1. **Infants (0-1 Year)**: Babies can be exposed to accidents such as falls and choking as their motor skills begin to develop. Especially falls from the bed or stroller are common in this age group.
2. **Young Children (1-3 years)**: As children in this age group begin to walk and climb, they face hazards such as climbing on furniture, playing with electrical outlets and touching hot surfaces.
3. **Preschool Children (3-5 years)**: As these children begin to move more independently, they may encounter various accidents in different parts of the house, such as the kitchen, bathroom and garden. Cuts, burns and poisoning are common in this age group.

The safety of the home environment plays a critical role in preventing home accidents. Hazards such as unsafe furniture, accessible toxic substances, hot surfaces and electrical outlets increase the risk of children being exposed to accidents.

The level of supervision of parents over their children and their awareness of safety is an important factor in the prevention of home accidents (Ablewhite vd., 2015). Parents' carelessness, fatigue or lack of knowledge about safety may increase the risk of children being exposed to accidents.

Table II: Common Fatal Home Accidents in Children

Falls are one of the most common types of home accidents in children. Stairs, beds, strollers and high furniture are places where children are particularly at risk of falling. Falls can lead to serious consequences such as head injuries, fractures and soft tissue injuries.
Burns can be caused by contact with hot surfaces, boiling liquids, electrical accidents and chemicals. Children may be at risk of burns by accessing sources such as hot water, teapots and irons, especially in the kitchen and bathroom. Burns can leave severe skin damage, infection and permanent scars (Şahin & Yilmaz, 2022).
Poisoning occurs when children accidentally swallow, inhale or come into skin contact with toxic substances. Cleaning agents, medicines, cosmetics and some plants pose a great risk when they are within the reach of children. Poisoning can cause nausea, vomiting, dizziness, seizures and, in severe cases, death.
Drowning can occur when children swallow small objects, fall into waterlogged areas or choke on something. Young children are at risk of choking on objects such as pieces of toys, food and coins. Drowning cases can result in respiratory failure, brain damage and death.
Cuts and injuries are caused by contact with cutting tools, broken glass, sharp corners and other sharp objects. Such accidents are particularly common in areas such as kitchens and bathrooms. Cuts carry a risk of infection and sometimes require stitches.

Prevention of home accidents is possible with the provision of a safe home environment and conscious actions of parents. Below are some strategies for the prevention of home accidents in children (Gielen, McDonald & Shields, 2015).

Creating a Safe Home Environment

1. **Furniture and Equipment Safety**: Securing furniture to the wall reduces the risk of climbing on high furniture. It is also important to keep cutting and piercing tools out of the reach of children.
2. **Electrical Safety**: Covering electrical outlets and organizing cords reduces the risk of electric shock to children. Electrical outlet covers ensure the safety of outlets.
3. **Protection from Hot Surfaces**: Protective barriers can be used in the kitchen and bathroom to limit access to hot water and surfaces. It is also important to keep teapot and pot handles facing inwards.
4. **Safety of Chemical Substances**: Cleaning agents, medicines and other chemicals should be stored in locked cabinets out of the reach of children. Legible labels and proper storage prevent accidents.

Parental Education and Supervision

1. **Information**: It is important to inform parents about safety precautions appropriate to the age and developmental level of children. Guidance brochures, training programs and online resources can be used.
2. **Active Supervision** Active supervision of children in playgrounds plays a critical role in preventing accidents. Careful and continuous observation by parents is essential.
3. **Emergency Plans**: It is important that parents know what to do in emergencies and can teach their children. Knowledge of first aid and easy access to emergency numbers ensures quick response in emergencies.

Safety Education for Children

It is important that children learn safety knowledge and skills appropriate for their age (Osborne vd., 2016). Identifying safe playgrounds, staying away from dangerous areas and introducing hazardous substances help protect children from accidents.

Management of Home Accidents and First Aid

The management of household accidents requires a quick and effective response. Knowledge of first aid is vital to minimize the negative consequences of accidents.

First Aid Basics

1. **Falls** After a fall, the child's consciousness should be checked and the child should not be moved. If a fracture is suspected, the area should be immobilized and emergency help should be called.

2. **Burns** Immediately wash the burn area with cold water and cover with a clean cloth. In case of severe burns, seek medical attention.
3. **Poisoning** In case of poisoning, check the child's breathing and consciousness, gather information about the poisonous substance and call for emergency help immediately.
4. **Choking** In case of choking, the Heimlich maneuver or other age-appropriate first aid methods should be applied. If the child is unconscious, CPR (heart massage and artificial respiration) should be started.
5. **Cuts and Injuries**: Clean cuts and stop bleeding. For deep cuts, seek medical attention.

Access to Health Services

Access to health services after household accidents is important depending on the severity of the injuries. Emergency services, family physicians and pediatricians play a critical role in the treatment of injuries resulting from home accidents. It is important that parents provide accurate information about their children's health status and follow medical recommendations (Gencer, Ozbek, Bozabali, Cangar & Miral, 2006).

Psychosocial Effects of Home Accidents

Home accidents can lead not only to physical injuries but also to psychosocial problems. Children and families may experience trauma, fear and anxiety after accidents.

Effects on Children

After accidents, children may show signs of trauma. These can include nightmares, sleep disturbances, changes in eating habits and fear. Psychological support can help children cope with this process.

Impact on Families

Parents may experience guilt, anxiety and stress due to their children's accidents. It is important for families to receive psychological support to cope with these feelings. In addition, taking the necessary steps to prevent accidents makes parents feel more confident about safety.

Community-Based Programs for the Prevention of Home Accidents

Prevention of household accidents should not be limited to individual efforts, but should also be supported by community-based programs. These programs can be carried out by public health institutions, educational institutions and non-governmental organizations.

Education and Awareness Campaigns

Raising awareness and educating the public about household accidents can help prevent accidents. These campaigns can be carried out through the media, schools and health institutions. Families can be informed about child safety and raised awareness about precautions to be taken at home.

Safe Home Projects

Community-based safe home projects can help families make their homes safer. Within the scope of these projects, home safety assessments can be conducted and safety equipment can be provided to families (Jones vd., 2018).

Health Policies and Regulations

Governments and local authorities can develop health policies and regulations to prevent household accidents. These policies may include measures such as setting product safety standards, disseminating child safety equipment and improving emergency services (Gielen, McDonald & Shields, 2015, Osborne vd., 2016, Turan, Dündar, Yorgancı & Yıldırım, 2010).

Conclusion and Recommendations

Home accidents in children are a common condition that can lead to serious health problems. Prevention and management of these accidents can be achieved by creating a safe home environment, raising parental awareness and providing safety education to children. In addition, community-based programs and health policies can play an important role in reducing home accidents.

Parents should be proactive about their children's safety and take necessary safety precautions at home. Educational institutions and health organizations can contribute to accident prevention by organizing safety education for parents and children. Future research can help to develop new strategies for the prevention and management of home accidents.

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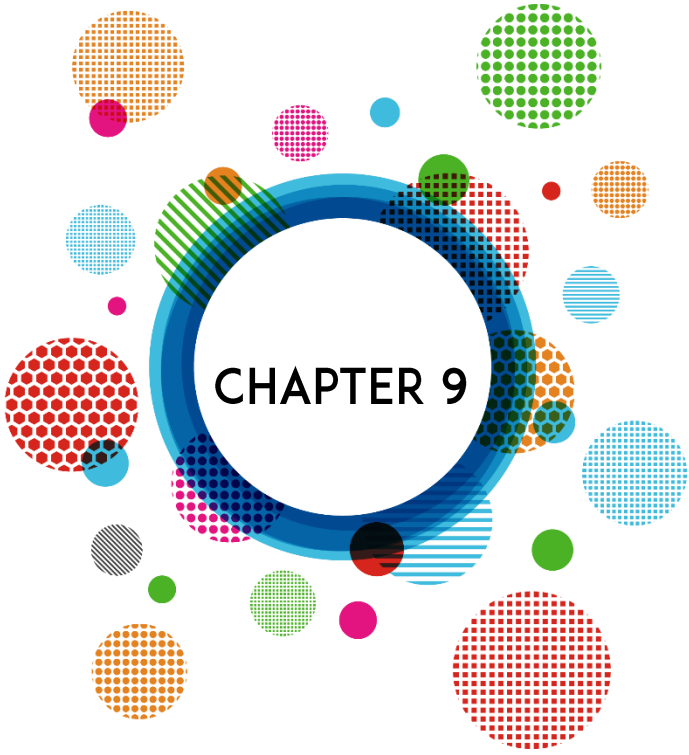

Current Approach to Halitosis

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INTRODUCTION

Halitosis is a word of Latin origin, derived from the combination of the word "halitus" meaning breathed air and the word "osis" meaning a pathological change. As a definition, it has the meaning of a foul smell spread from the breath. Other terms used to explain this word are oral malodour, mouth odour, fetor narium, bad breath, and fetor ex ore (Aylıkcı and Çolak, 2013).

It can be seen that halitosis has a very long history with examinations from a thousand years ago. As there was no medical treatment at that time, folk remedies for this complaint have included parsley (Italy), cloves (Iraq), guava peel (Thailand), and egg shells (China) (Scully and Felix, 2005).

The current widespread use of social media, higher standards of aesthetic understanding, and the efforts of individuals to be accepted, have led to the social exclusion of individuals with halitosis (Silva et al.,2018). Bad breath is a serious problem associated with diminished quality of life. This problem is a social barrier that is a reason for the individual to withdraw from society (Quirynen et al.,2009). Individuals who are aware of this condition experience psychological embarrassment and this leads to depression. Those who develop tolerance or smell disorders may not be aware of the condition, in which case they may be told by the family or those around them that they have halitosis. The reluctance of people in their social environment to say that they have halitosis can cause them to live with bad breath for their entire lifetime (Abulwefa and Abushoufa, 2020).

HALITOSIS TYPES

Understanding the origin of halitosis is of great importance in determining appropriate treatment. When examined according to origin, there are three categories of real halitosis, pseudohalitosis, and halitophobia. Real halitosis is seen with an advanced degree of evident oral malodour and is classified as physiological and pathological (Gülşen, 2012).

Physiological halitosis manifests with bad breath in the morning. Accumulation of food particles on the tongue causes the formation of bacteria and the odour decreeases with fluid intake (Porter and Scully, 2006). Alcohol consumption, smoking, and consumption of garlic, onions, and spicy foods affect the development of physiological halitosis, which can be completely eliminated with good oral hygiene (Anbardan et al., 2015).

Pathological halitosis generally develops due to a pathological reason and is almost impossible to reverse. It is a permanent disease, which cannot be corrected regardless of however much effective brushing is performed. Pathological halitosis can develop in association with many intra and extra-oral reasons. It mostly emerges as a result of gram-negative anaerobic bacteria activity (Porter and Scully, 2006;

Outhouse et al., 2006). Bacteroides, Eubacterium, Fusobacterium, Peptostreptococcus, Porphyromonas, Selenomonas, Veillonella, and Tannerella forsythia are responsible for the production of hydrogen sulfur and most of these bacteria play an important role in the pathogenesis of periodontal diseases (Hampelska et al., 2020).

As can be understood from the name, pseudohalitosis is a false oral odour. Even if the patient states how much of a problem this is, these are conditions that can be brought under control with minor treatments, and will generally recover by convincing the patient on this subject. In halitophobia, patients insist that they are ill despite the absence of bad breath (Gülşen, 2012).

Another classification of extra-oral halitosis types is non-blood-borne halitosis, which develops because of a disorder in any part of the body and the bad smell is spread via the lungs, as seen in hepatic cirrhosis. In blood-borne halitosis, the sources of the bad smell are the nose, paranasal or laryngeal regions, the lungs, or upper digestive system (Abulwefa and Abushoufa, 2020). Following these classifications, the current classification system is:

Type 0 (physiological) Type 1 (oral)

Type 2 (airway) Type 3 (gastroesophageal)

Type 4 (pathological/ via blood) Type 5 (subjective)

With the exception of Type 0, all other halitosis types are considered pathological.

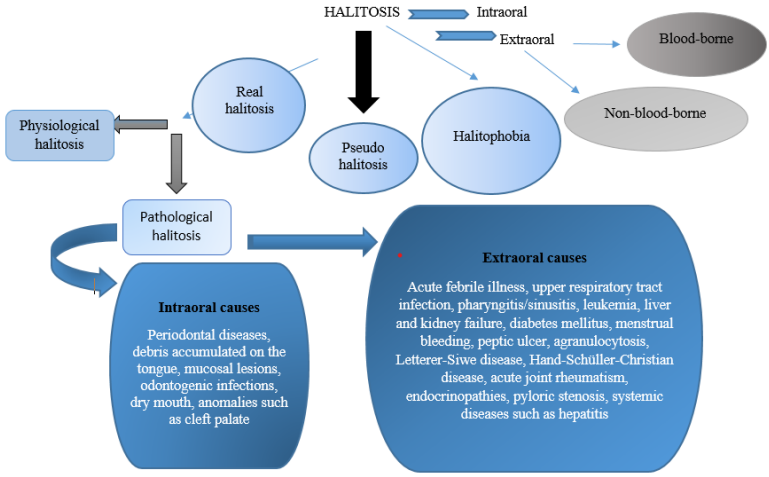

Figure 1. Halitosis types

CONTENT OF HALITOSIS

The main cause of oral odor is volatile sulfur compounds, the most important of which are hydrogen sulfur (H2S), methyl mercaptan (CH3SH), and dimethyl sulfide (CH3SCH3) (Bicak, 2018). In addition, many substances causing a bad smell such as methanol, acetone, phenol, pentanes, ethanol, indole, diamines, and short-chain fatty acids are found in the saliva, but are not perceptible at low concentrations (Quirynen et al., 2009; Haraszthy et al., 2007).

Bacteria play a major role in halitosis formation. The bacteria producing volatile sulphur compounds which are isolated most from individuals with halitosis are Treponema denticola, Tanneralla forsythia, Actinobacilli, Porphyromonas gingivalis, Fusobacterium nucleatum, Prevotella intermedia, and Prevotella nigrescens. Other bacterial strains associated with periodontal disease with a high capacity to produce volatile sulfur compounds include Tannerella forsythia, Fusobacterium periodonticum, Eikenella corrodens, and Centipeda periodontii from the Enterobacteriaceae family (Hampelska et al., 2020).

The production of volatile sulfur compounds, and the presence of sufficient infrastructure for the metabolism of bacteria other than the production of bacteria depends on many local factors such as saliva (fluidity, pH, and mount) and reduced oxygen concentration.

THE PREVALENCE OF HALITOSIS

It is extremely difficult to evaluate the prevalence of halitosis because of the low number of community-based studies on this subject (Hughes, 2008; Scully and Greenman, 2012). For reasons such as differences in smell perception between individuals of different races and cultures, and that evaluations are not standardized, differences are seen in the general worldwide prevalence of halitosis (Liu et al., 2006; Cortelli et al., 2008). It has been reported that halitosis is observed in >10% of the population in many countries (Iwanicka-Grzegorek, 2005; Tessier, 1991).

Some of the factors effective in the determination of the exact prevalence of halitosis are age, gender, diseases, oral hygiene, dental health, medications, food, and smoking. The source of halitosis is the oral cavity in 90% of patients, and extra-oral reasons in 9%. These include respiratory, gastrointestinal and urinary systems. Diet and medications constitute the reasons for halitosis in 1% of patients (Aylıkcı and Çolak, 2013).

From an examination of the research in literature, age and gender are seen to be more effective parameters in most studies. Studies conducted to determine differences between the genders have generally shown a similar prevalence of halitosis (Farah, 2019; Aimetti, 2015). In the USA, a mouth spray is used by 60% of females and 50% of males for this complaint. When age groups have been evaluated, it can be seen that all age groups are affected and the frequency increases with age.

A study in the Netherlands reported that halitosis is one of the 100 most common complaints (Bollen and Beikler, 2012), and another study in Brazil found that halitosis is more common in males and the elderly (32). Al-Ansari et al. evaluated 1500 individuals and determined halitosis in 25% of them (Al-Ansari et al., 2006). In a study of 2000 subjects in China, Liu et al. also showed this rate to be 25% (Liu, 2006). Another study of 840 males in Sweden determined halitosis at the rate of 2% (Söder, 2000). A study in Jordan that included individuals aged 18-68 years found that halitosis was diagnosed in 78% of the study population (Hammad et al., 2014). Another study in the USA reported that 24% of individuals aged ≥60 years complained of halitosis (Birkent and Şölen, 2005). The prevalence of halitosis was determined to be 37% in another study of the 11-12 years age group (Haghgoo and Abbasi, 2013; Villa et al., 2014). When this subject was investigated in dentistry students, the rate of halitosis was observed to be lower than that in the general population (Al-Rawi and Al-Atrooshi, 2007; Paradowska and Marczewski, 2007). The reason for this was thought to be greater knowledge and awareness of this subject.

In a study by the International Association for Halitosis Research (IAFHR), it was stated that psychological problems due to halitosis are experienced by approximately 8% of the world population (Scully and Greenman, 2012).

Throughout the world in general, halitosis is the third most common reason for visiting a dentist after tooth decay and periodontal disease. In the USA, 41% of dentists stated that at least 6 patients per week presented at clinics because of halitosis (Birkent and Şölen, 2005). A previous study in Türkiye examined the data of 459 patients aged >18 years. Oral health, the periodontal status, plaque and gingival indexes, and deposits on the tongue surface were evaluated in respect of halitosis, and it was concluded that there was evidence of halitosis in 50.7% of the patients (Keriş et al., 2016).

THE ETIOLOGY OF HALITOSIS

Various statements and discussions regarding the causes of halitosis have been made in the past. While dentists have emphasized oral reasons, reluctance regarding the subject of treatment has encouraged them to explain extra-oral reasons. Studies have shown that the mouth is the source of halitosis in the majority of cases (Kapoor et al., 2016).

The causes of real halitosis include oral and systemic factors. In 80% of cases, the source is intra-oral, for reasons including poor oral hygiene, gingival inflammation, gingivitis, periodontitis, reduced saliva expression, oral aphtosis, inflammation of the tonsils, pericoronitis, peri-implantitis, necrotic dental pulp, and xerostomia (Bollen and Beikler, 2012). An increase in dry mouth causes progression to more severe halitosis.

Drugs have come to the fore, especially for those experiencing dry mouth for a long time. The use of several medications together by elderly patients creates a synergistic effect, increasing the likelihood of experiencing dry mouth. More than 500 drugs may cause dry mouth, including anorexiants, anticholinergic/antispasmodic agents, anticonvulsants, analgesics, anti-Parkinson's drugs, antipsychotics, bronchodilators, chemotherapy agents, decongestants, diuretics, and sedatives. It has been seen that an increase in the dosage of these drugs is correlated with a further increase in dry mouth, and thus complaints of halitosis increase in these patients.

Patients presenting at a specialist clinic in Belgium were evaluated in respect of halitosis, and it was observed that the source of halitosis was the mouth (87%), as periodontitis in 60%, and the tongue in 40%. Therefore, dentists are responsible for the diagnosis and treatment of halitosis (Delanghe et al., 1997).

Extra-oral factors related to systemic diseases constitute 10-20% of halitosis cases (Memon et al., 2023). This classification includes diabetic ketoacidosis, liver failure, cirrhosis, tuberculosis, kidney failure, uremia, various gastrointestinal disorders, irregular bowel movements, trimethylaminuria – drug use, hormonal reasons, duodenal obstruction, sinusitis, tonsillitis, and nasal polyps. Eating onions, garlic, and spices, smoking, and drinking alcohol create temporary halitosis,which may be mistaken for real halitosis, but when their use is terminated, the alodourous effect is eliminated within a few hours (Van den Broek et al., 2007).

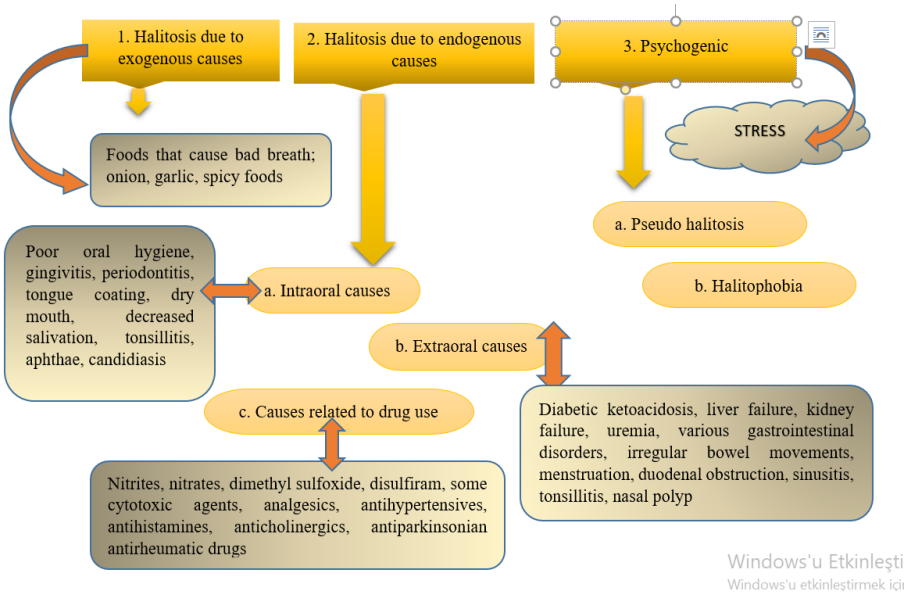

Figure 2. Etiology of halitosis

EXAMINATION OF HALITOSIS

The international consensus group recommends the two basic methods of organoleptic measurement and instrumental measurement for the clinical determination of halitosis.

Organoleptic measurement is the simplest and most widely used method. This is a subjective evaluation which is performed by smelling the breath of the patient and scoring the level of oral malodour. The examiner smells the mixture of oral air and alveolar air, which is not a pure air sample, and the examination cannot differentiate between them. For a reliable diagnosis, evaluation of the oral odor should be made on two or three different days. This method is important, especially when pseudohalitosis or halitophobia is suspected (Erhamza and Çarpar, 2020).

To be able to make a correct evaluation, it is important that the examiner does not smoke, does not use perfumed cosmetics, has asthma or chronic allergies, and does not drink tea, coffee, or fruit juices before the procedure. The criteria defined for the patients before the evaluation were as follows;

Not to have taken antibiotics in the previous 3 weeks,

Not to have eaten foods such as onions or garlic in the previous 48 hours,

Not to have used perfumed cosmetics within the previous 24 hours,

Not smoking within the previous 12 hours (Aydin and Harvey-Woodworth, 2014).

Category	**Explanation**
0: No smell	Smell cannot be determined
1: Suspicous smell	There is a smell that cannot be perceived as a bad smell by the examiner
2: Slightly bad smell	A smell is present that can definitely be determined but which is weak
3: Moderately bad smell	There is a bad smell that is possible to detect
4: Strong bad smell	There is an overwhelming smell that is very distrurbing to the examiner
5: Severe bad smell	There is an excessively bad smell that cannot be tolerated by the examiner who instinctively turns up or covers his nose

Table 1. Organoleptic scoring scale (Şeker and Tumer, 2014)

Instrumental measurement is an objective method for the measurement of volatile sulfur compounds which are the basic components of oral malodour. Two devices

are used for this purpose: Halimeter® and OralChroma™ (Göktürk and Devrim, 2014). This measurement method can be reliably used, especially in patients with the complaining of psychogenic oral odour.

Halimeter: This is a low-cost, easy-to-use objective test. The volatile sulfur compounds were measured using an electrochemical sensor (Erhamza and Çarpar, 2020). This was performed using a probe for the device to reach air. The halimeter has high sensitivity for hydrogen sulfur, but low sensitivity for methyl mercaptan, which causes oral malodour in patients with periodontal disease (Salako and Philip, 2010).

Oral Chroma: In this device, which only measures defined gases, material is taken from the mouth with a syringe and placed in the device, and the measurement is completed after 8 min. It provides three different values for hydrogen sulfur, dimethyl sulfide, and methyl mercaptan (Göktürk and Devrim, 2014)

HALITOSIS TREATMENT

The first step required in the treatment of halitosis is to eliminate the source of the oral malodour. The initial treatment should aim to reduce the intra-oral bacteria, and to achieve this it is necessary to improve the oral hygiene of the patient. Mechanical tongue cleaning should be performed first. Professional tongue cleaning significantly decreases oral malodor (Zürcher et al., 2014).

Correct alignment of the teeth is also important to ensure that entrapped food particles do not create malodour. Toothpastes containing zinc, mouthwashes, synthetic saliva preparations, mint tablets, tongue cleaners, and chewing gum are sold for this purpose (Wu, 2020). The use of these products can mask halitosis for a short time however, this is not a permanent solution. The use of these products to increase saliva expression can also prevent halitosis.

If halitosis is caused by problems such as dental decay, insufficient dental restorations, or gingival problems such as gingivitis or periodontitis, treatments aimed at these causes are initiated (Anbardan et al., 2015). After oral hygiene, dental examinations must be performed twice a year and feedback on complaints must be obtained.

If the source is extraoral, the patient should be referred to an Ear, Nose, and Throat specialist for tests for pathologies such as upper or lower respiratory tract infection, tonsillitis, or nasal obstruction. If no problem is detected as a result of this examination, the patient must be referred to an Internal Diseases specialist for evaluation of gastrointestinal diseases. Endoscopic imaging is performed for diagnostic purposes.

Treatment in the early period can be made under the guidance of a psychologist for mental health disorders caused by halitosis (Akpata et al., 2009). The treatment

process can be accelerated with a multidisciplinary approach of healthcare service providers together with psychologists and psychiatrists (Kapoor et al., 2016).

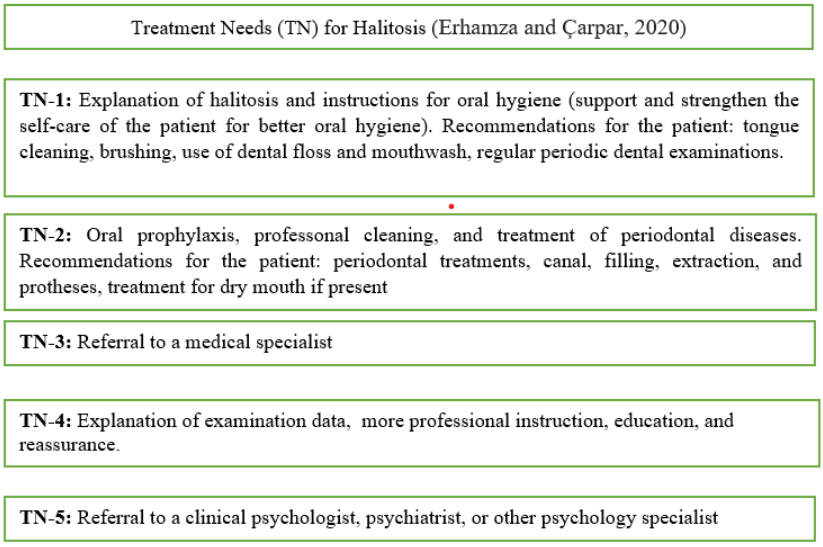

Figure 3. Treatment needs for halitosis

CONCLUSION

Halitosis is a disease that has a severe negative effect on the life and psychology of the individual. Therefore, when treating this disease, the causes must be questioned in detail, and when necessary, recommendations must be made for the use of suppressive agents.

As this disease has an intraoral source in 80-90% of cases, patients must be informed of the need to see a dentist. The remaining 10-20% of cases develop due to extra-oral reasons. One way to understand the actual pathophysiological process is to increase medical awareness. Consistent application of the diagnosis and treatment concepts will increase treatment success to a high level.

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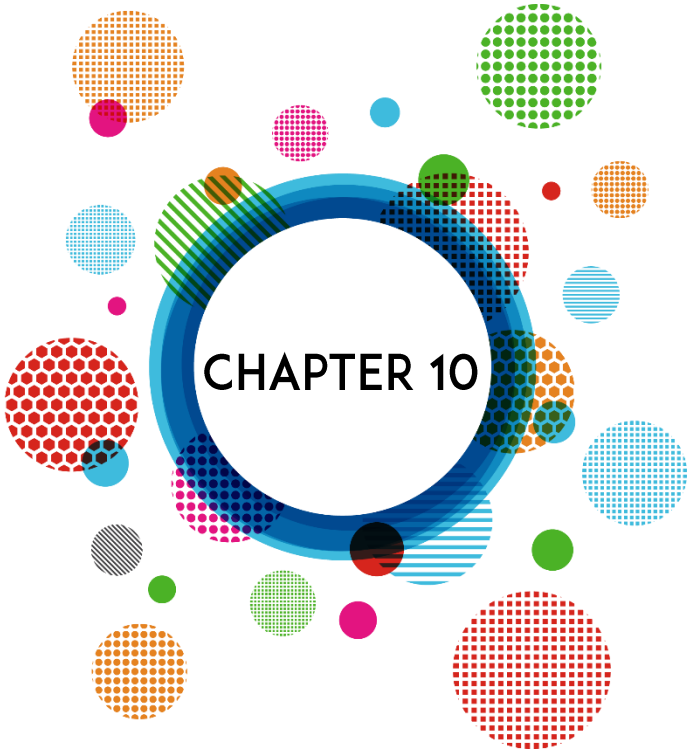

Psychological Measurement Techniques and Applications: A Comprehensive Overview of Traditional and Artificial Intelligence Utlizations

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People encounter many situations in daily life including instances where we struggle to articulate our thoughts, crises, sicknesses, and periods of stress.

This chapter outlines how science and technology help both athletes and the general population manage stress, anxiety, and arousal. Regulating our responses to unfamiliar situations predominantly stems from awareness. Self-awareness necessitates a profound understanding of oneself, comprising a multitude of psychological aspects. When it comes to self-awareness, it is essential for individuals to have a comprehensive understanding of themselves, which is a result of a variety of psychological factors. Arousal regulation is achieved through methods that promote awareness and balance, integrating physiological, cognitive, emotional, and environmental factors. In the literature and technological advancements, there are numerous methods and applications for noticing, defining, developing strategies, implementing, providing feedback, and self-learning.

The methodologies and their applications have examined in a broad framework that resources on sports and recreation available for individual use will be succinctly examine. After discussing the age group distinctions in various sports, we will talk about Arousal Regulation and Situational Awareness Management, which individuals should pay attention to in general public health. (Artificial intelligence has been used in our study). Our analyses expressing the developments in methods and applications with artificial intelligence are evaluated in the section following the Arousal Regulation method. In the other section, comparisons and theoretical foundations between artificial intelligence and conventional methods will be presented.

Psychological Measurement Methods and Applications (Assessment Tools & Apps)

Some applications used with today's technologies are listed below. In tracking mood, stress, endurance, recovery, sleep state, attention, and mental state.

Applications (Apps)

Mindletic: Helps athletes track their mood and enhance their mental resilience. Includes daily mood tracking and exercises.

Whoop: Measures stress levels, sleep quality, and recovery rates along with physical performance. It provides data related to psychological conditions.

HRV4Training: Analyzes stress and recovery status through heart rate variability (HRV). It is also used as an indicator of mental state.

mHealth applications (for example, Calm, Headspace): Used to track and improve stress, anxiety, attention, and sleep conditions.

Psychological Measurement Tools (Surveys/Scales)

Tools used to manage athletes' mental resilience, stress, and anxiety levels;

Sport Mental Toughness Questionnaire (SMTQ): Measures mental toughness.

Athletic Coping Skills Inventory (ACSI-28): Measures coping skills in athletes.

Competitive State Anxiety Inventory-2 (CSAI-2): Commonly used to measure pre-competition anxiety levels.

Resilience Scale for Adults (RSA) or Brief Resilience Scale (BRS): Measurement of psychological resilience.

Flow State Scale (FSS): Measures the flow experience (flow state).

Attention and Performance Scales (TAP): Digital tests used to measure concentration and attention performance.

Psychological Development and Intervention Methods (Developmental Practices)

Mental Training Techniques

Imagery / Visualization: The athlete mentally visualizes a movement or competition.

Goal Setting: Performance enhancement with SMART goals.

Self-Talk: Increasing motivation and self-confidence through positive internal dialogues.

Focus and Concentration Techniques: Exercises to maintain attention.

Biofeedback: It teaches you to control biological indicators, especially heart rate, breathing, and muscle tension.

Mental Health and Mindfulness (Mindfulness & Recovery**)**

Mindfulness Meditation: Reducing stress, increasing focus.

Breathing Techniques: Calming by activating the parasympathetic system.

Progressive Muscle Relaxation (PMR): Provides relaxation by sequentially relaxing muscle groups.

Yoga & Tai Chi: Provides both physical and mental flexibility.

Digital Education and Consulting Platforms

BetterUp: Offers one-on-one sessions for coaching and mental performance development.

Sport Psychology Today: Sports psychology content, exercises, and application suggestions.

BelievePerform: Offers infographics, articles, and development videos for athletes.

PsychEdge: Offers specialized digital programs to enhance athletes' mental skills.

Systems Used for the Team

AMS (Athlete Management Systems): (Ex: Kitman Labs, Smartabase) – Tracks holistic health data, including the athlete's psychological condition.

Coach-supported mental skills programs: Mental skills training is integrated during sport-specific training sessions.

Psychological measurement and development tools for amateur and professional athletes

Psychological Measurement and Development Methods for Amateur Athletes.

Sports psychology aims to enhance athletes' motivation, commitment, and learning processes through targeted mental strategies. In sports psychology, the aim is to teach, enhance motivation, and strengthen commitment to the sport.

Measurement Tools

• ACSI-28 (Athletic Coping Skills Inventory): It is suitable for evaluating the coping strategies of individuals who are new to sports.

• SMTQ (Sport Mental Toughness Questionnaire) – Simplified versions can be used with young or amateur athletes.

• Flow Short Scale (FSS-2 Short Form): Evaluation of flow state with simple and applicable measurements.

• Mindfulness Attention Awareness Scale (MAAS): Measures daily mindfulness levels.

• Adaptive self-assessment forms: Short psychological condition questionnaires adapted by coaches.

Development Exercises

• Basic breathing and relaxation techniques

• Simple visualization exercises (for example, a mental rehearsal of the pre-competition routine)

• Positive self-talk cards (example: "I can do it", "I'm ready")

• SMART goal-setting workshops

• Mindfulness-based applications (e.g., Headspace Kids/Teens)

Psychological Assessment and Development Methods for Professional Athletes

Performance stability, decision-making under high pressure, and the optimization of recovery processes are aimed at.

Measurement Tools

• CSAI-2 (Competitive State Anxiety Inventory): Used to analyze pre-competition anxiety levels.

• TAMI (Test of Attentional and Interpersonal Style): Attention control and interpersonal skills.

• Heart Rate Variability (HRV) applications (e.g., HRV4Training, WHOOP): The relationship between mental stress and physiological feedback.

• Resilience Scale for Athletes: Psychological resilience scales, adapted versions for elite athletes.

• Sport Psychology Profiling (e.g. Sport Psychology Performance Profile): Individual psychological skill inventories.

Development Exercises and Programs

• Advanced mental training protocols:

o Intense visualization techniques (example: match scenario, crisis resolution, comeback scenario)

o Mental set transition exercises (adjusting arousal levels)

• Stress control with biofeedback and neurofeedback systems

• Performance-specific mindfulness practices (example: MAC – Mindfulness-Acceptance-Commitment Model in Sport)

• Periodization integrated with psychological skills training (synchronized with sports training)

• Cognitive restructuring through crisis scenarios

Psychological Measurement and Development Tools According to Sport Branch and Age Group

Age Group: Child and Adolescent Athletes (8–17 years)

It aims to strengthen the habit of sports, develop self-confidence, motivation, and attention skills, and teach how to manage training/competition anxiety.

Table 1. Measurement Tools

Measurement Tool	**Description**	**Level**
CSAI-2C (Adapted Children's Anxiety Scale)	Measures pre-competition anxiety levels	Amateur
Children's Sport Self-Efficacy Scale	Sports self-efficacy	Amateur
Mindfulness for Children Questionnaire (MFQ-C)	Flow	Both levels
KIDSCREEN-10 (Quality of life)	Measures psychological well-being	Both levels

Developmental Tools:

• Game-based attention-enhancing exercises (example: "visualization with charades")

• Short-term breathing games (example: breath control with "blowing a balloon" technique)

• Child-friendly meditation apps (Headspace Kids)

• Goal-setting coloring cards (visual SMART goals)

Age Group: Young Adult Athletes (18–25 years old)

Aims to focus on performance goals, develop anxiety tolerance, and improve individual and team communication.

Table 2. Measurement Tools

Measurement Tool	Description	Level
ACSI-28 Coping skills Both levels	Coping skills	Both levels
SMTQ Mental	toughness	Amateur/professional
FSS-2 Flow level Professional	Flow	Professional
MACS (Motivation Analysis of Competitive Sports)	Motivation analysis Amateur	**Amateur**

Development Tools:

• Mental rehearsal against competition scenarios

• Journaling exercises on attention and emotional control

• Performance breathing & 4-7-8 technique

• Individual work with visualization audio recordings

Age Group: Adult Athletes (25 years and older)

Sustained performance under high stress, Leadership, decision making and team Synergy, Mental recovery and post-injury recovery are targeted.

Table 3. Measuring Tools

Measurement Tool	**Description**	**Level**
CSAI-2 Pre-competitive	anxiety	Professional
RSA / BRS Psychological resilience Both levels	RSA / BRS Psychological resilience Both levels	RSA / BRS Psychological resilience Both levels
TAMI Attention and interpersonal style measurement Professional	TAMI Attention and interpersonal style measurement Professional	TAMI Attention and interpersonal style measurement Professional
HRV applications (Whoop, EliteHRV) Biological stress – psychological reflection Professional	HRV applications (Whoop, EliteHRV) Biological stress – psychological reflection Professional	HRV applications (Whoop, EliteHRV) Biological stress – psychological reflection Professional

Developmental Tools:

• MAC (Mindfulness-Acceptance-Commitment) Based Interventions

• Cognitive restructuring for crisis and pressure scenarios

• Relaxation training with biofeedback devices

• Advanced goal simulations (example: for Olympic/championship preparation)

Differences Based on Sports Branch (Selected Examples)

Applications differ according to the sport being performed.

Table 4. Sport branch intervention

Sport	**Psychological Emphasis Recommended**	**Intervention**
Individual sports (swimming, track and field)	Focus, self-regulation Self-talk + visualization	Self-talk + visualization
Team sports (soccer, basketball)	Communication, group cohesion	Group goal setting + social support activities
Aesthetic sports (artistic gymnastics, ice skating)	Stage anxiety, self-perception	Visualization + body awareness
Combat sports	Arousal management, anger management	Breathing + mental transition techniques
Endurance sports (marathon, triathlon)	Patience, intrinsic motivation	Mindfulness-based strategies + internal dialogue

Situational Awareness Management and Arousal Regulation

The concept of arousal means forcing any organ of a living being to perform a task with an external effect, telling it to behave (Tdk, 26.05.2025). Arousal refers to the physiological and psychological activation level of the individual. Optimal arousal is the point at which the individual performs best. Low arousal: Lack of motivation, distraction, low energy, Medium arousal (ideal zone): Focused attention, mental clarity, high performance, Over-arousal: Tension, panic, lack of coordination (Weinberg, Gould, 2015). Situational awareness is the ability of an individual to perceive important information in their environment, to make sense of this information, and to predict future situations. It has been said to occur in the stages of perception, comprehension, and projection (Endsley, 1995). Below, tools and methods that measure slow movement, attentional awareness, situational awareness, arousal through desire and observation, and situational awareness are discussed.

Table 5. Arousal Regulation

Scale Name	Description	Reference
CSAI-2 / CSAI-2R (Competitive State Anxiety Inventory)	Cognitive, somatic anxiety and self-esteem components Martens et al., 1990	Martens et al., 1990
SCAT (Sport Competition Anxiety Test)	Measures athlete anxiety	Martens, 1977
SAS (State Arousal Scale)	Measures momentary arousal level	Thayer, 1989
POMS (Profile of Mood States)	Monitors emotional states such as energy and tension	McNair et al., 1971
RESTQ-Sport	Recovery and stress profile for athletes	Kellmann & Kallus, 2001

Table 6. Situational Awareness and Introspection

Scale Name	Description	Reference
MAAS (Mindful Attention Awareness Scale)	Daily awareness level	Brown & Ryan, 2003
SAC (Situational Awareness Rating Technique)	Situational awareness level measurement	Endsley, 1995
Toronto Alexithymia Scale (TAS-20)	Difficulty in recognizing and noticing emotions	Bagby et al., 1994

Situational Awareness Management and Arousal Regulation Applications and Mobile Applications (Apps)

Individual strategies that each individual can employ include the management of physiological data, such as respiratory rate and sensory awareness (feeling energized), the use of mottos that are beneficial for the mood, the use of art tools and visualization, and the use of shouting and laughing therapies.

Table 7. Applications and Mobile Applications (Apps)

Application	**Features**	**Usage**
Headspace / Calm	Breathing, relaxation, awareness exercises	Athletes and students
Breathe+ / Breathwrk	Breath regulation, arousal control	Pre-performance
HRV4Training / WHOOP	Heart rate arousal tracking	Professional level athletes
Primed Mind	Voice prompts for mental preparation and relaxation	Customized visualization
Smiling Mind (Sport program)	Athlete-specific awareness training	Team or individual

Methods, Exercises, Intervention Techniques

The following list includes cognitive, physiological, and situational or awareness-related regulations for identifying anxiety-inducing situations. The ability to regulate our energy level has a synergistic influence on mood control and skill development (Weinberg, Gould, 2015).

Arousal Regulation (Downregulation / Upregulation)

1. Diaphragmatic Breathing Exercises

o 4-7-8 technique, box breathing (Lehrer et al., 2000)

2. Progressive Muscle Relaxation (PMR)

o Muscle relaxation with the Jacobson technique (Jacobson, 1938)

3. Biofeedback & Neurofeedback

o Stress management through heart rhythm and brain waves o (Peper et al., 2008)

4. Mindfulness-Based Interventions (MBSR, MAC Model)

o Mental flexibility and arousal management (Kabat-Zinn, 1990), (Gardner & Moore, 2007)

5. Arousal Zoning Exercise

o Recognizing the individual's performance-peak arousal level

o Example: "Zone of Optimal Functioning (ZOF)" (Hanin, 2000)

Table 8. Situational Awareness Development Methods

Method	**Description**	**Reference**
Mindfulness-Based Sports Training (MAC)	Acceptance and awareness-based mental training	Gardner & Moore, 2007
Imagery + Internal Observation	Imagery + Internal Observation Mental preparation with previously rehearsed scenarios	Cumming & Williams, 2012
Mindfulness Diary	Mindfulness Diary Monitoring the emotion-thought-practice trinity	Kabat-Zinn, 1990
Situational Scenarios Simulations	Situational Scenarios Simulations Mental rehearsal in real match/stress scenarios	Vealey, 2007
"STOP" technique (Pause → Observe → Proceed)	Pause exercise in the face of sudden arousal	Crane et al., 2017

To give an example of one of the methods we mentioned above, the "STOP" Technique Stages to be used in moments of intensity and crisis are listed as both awareness and situation management stages (Crane et al., 2017).

Table 9. "STOP" technique

Stage	**Description**
S – Stop	Whatever you are doing, stop for a moment. This can be a physical or mental pause. It is the first step to preventing automatic, habitual reactions from taking hold.
T – Take a Breath	Consciously take a deep breath. This helps regulate the nervous system (increase parasympathetic activation) and facilitates awareness of the moment.
O – Observe	Observe your internal and external experience: feelings, thoughts, bodily sensations, and what is happening around you. Ask questions such as, “What am I feeling right now? What is happening in my body?”
P – Proceed	Now proceed consciously and purposefully. Choose your response, and consciously implement the action that is most appropriate to the situation.

Theoretical Framework

The theories enumerated below are derived from measurements and applications developed by commonly utilized traditional and artificial intelligence, as a consequence of the literature review. It also provides the basis for future applications.

1. Arousal and Stress Theories

Yerkes-Dodson Law: This theory suggests that performance increases with arousal up to a certain point, after which further increases in arousal can impair performance. It helps to assess the optimal arousal levels for athletes and how they affect performance (Yerkes, Dodson, 1908).

Inverted-U Hypothesis: Similar to Yerkes-Dodson Law, this model posits that there is an optimal level of arousal for peak performance and either too little or too much arousal can negatively impact performance.

Cognitive Anxiety Theory: This theory focuses on how the mental state of anxiety (cognitive and somatic) can affect sports performance and how athletes manage stress and anxiety levels during competition (Martens et al, 1990).

2. Motivation Theories

Self-Determination Theory (SDT): Developed by Deci and Ryan, this theory emphasizes intrinsic and extrinsic motivation and how they influence athletes' engagement and performance. It is used to assess the sources of motivation and their impact on athletic behavior (Deci, Ryan, 1985).

Achievement Goal Theory: This theory examines the different goals that athletes may pursue, such as mastery goals (focus on skill improvement) versus performance goals (focus on comparing oneself to others). It helps to quantify athletes' goal orientations and their effect on performance (Nicholls, 1989).

Attribution Theory: This theory looks at how athletes attribute their successes or failures (e.g., to internal factors like effort or external factors like luck). It is used to understand how athletes' perceptions of success or failure influence their motivation and future performance (Weiner, 1985).

3. Personality Theories

Big Five Personality Traits: This model assesses five broad personality traits—openness, conscientiousness, extraversion, agreeableness, and neuroticism—often used in sports psychology to understand athletes' personality profiles and their correlation with performance outcomes (Mcrae, Costa, 1999).

Eysenck's Personality Theory: Focuses on how personality traits, particularly introversion/extroversion and emotional stability, influence athletic performance, with particular emphasis on stress management and arousal levels (Eysenck, 1967).

Hardiness Theory: Developed by Kobasa, this theory assesses psychological resilience and how athletes' hardiness (commitment, control, and challenge) influences their ability to cope with stress and perform under pressure (Kobasa, 1979).

4. Cognitive and Mental Skills Theories

Information Processing Theory: This theory explores how athletes process information, make decisions, and react in competitive settings. It's used to quantify reaction time, decision-making accuracy, and the impact of cognitive load on performance (Welford, 1968).

Cognitive Behavioral Theory (CBT): Focuses on how thoughts, emotions, and behaviors interact. In sports, CBT is used to address issues like performance anxiety, self-doubt, and negative thinking, and can be quantitatively measured through cognitive-behavioral interventions (Beck, 1976).

Mental Toughness Theory: Mental toughness is assessed through factors like focus, resilience, and emotional control. This theory evaluates how an athlete's mental fortitude influences their ability to perform under pressure (Clough,Sewell, 2002).

5. Flow Theory

Csikszentmihalyi's Flow Theory: This theory explains the optimal state of intrinsic motivation where an athlete is fully immersed in their performance, experiencing heightened focus, creativity, and skill utilization. Quantifying flow states can help assess how athletes achieve peak performance and how these states impact outcomes (Csikszentmihalyi, 1990).

Flow State Scale (FSS): A quantitative tool to measure the presence of flow in athletes during practice or competition, focusing on factors like concentration, skill-challenge balance, and intrinsic motivation (Jackson, Marsh, 1996).

6. Self-Efficacy and Confidence Theories

Bandura's Self-Efficacy Theory: Self-efficacy, or the belief in one's ability to succeed in specific situations, is a major determinant of performance. Bandura's theory is used to assess athletes' confidence and how it affects their performance, with measurements often based on self-report scales and behavioral observations (Bandura, 1997).

Sport Confidence Model: This model looks at how athletes' confidence in their skills influences their overall performance. Quantitative assessments often use measures like the Sport Confidence Inventory (Vealey, 1986).

7. Self-Regulation and Goal Setting Theories

Locke and Latham's Goal Setting Theory: This theory focuses on the role of specific, challenging, and attainable goals in enhancing performance. It is commonly used to assess athletes' goal-setting behaviors and their impact on motivation and performance (Locke, Latham, 1990).

Self-Regulation Theory: Focuses on how athletes control their thoughts, emotions, and behaviors to achieve goals. It is used to quantify self-control, focus, and persistence, particularly during challenging circumstances (Carver, Scheier, 1982).

8. Social and Team Dynamics Theories

Social Cognitive Theory: This theory emphasizes the influence of observational learning, imitation, and modeling on behavior. In sports, it is used to understand how athletes learn from coaches, teammates, and competitors (Bandura, 1986).

Team Cohesion Theory: Team cohesion is critical for team sports, and this theory examines how interpersonal relationships and group dynamics contribute to team performance. Theories like Carron's Model of Group Cohesion assess both task cohesion (focus on team goals) and social cohesion (relationships between team members) (Carron, Brawley, 1998).

9. Resilience and Coping Theories

Lazarus and Folkman's Stress and Coping Theory: This theory explores how athletes cope with stress, specifically in relation to competitive performance. It is used to assess the coping strategies employ athletes and how they influence their performance outcomes (Lazarus, 1984).

Resilience Theory: This theory is used to quantify an athlete's ability to recover from setbacks, adapt to challenges, and continue performing under adversity (Masten, 2001).

10. Emotional Regulation and Control Theories

Gross's Emotion Regulation Theory: This model focuses on how athletes manage their emotions before, during, and after competition. It helps in quantifying emotional responses and the strategies athletes use to maintain composure and focus (Gross, 1998).

Elliot's Approach-Avoidance Motivation Theory: It looks at how athletes are motivated to either approach success or avoid failure, which can influence their emotional regulation and performance (Elliot, 1999).

These theories and frameworks are used in combination with quantitative tools, such as surveys, psychometric tests, performance metrics, and behavioral observations, to assess the psychological states and traits of athletes. They help

coaches, sports psychologists, and researchers understand and optimize the mental aspects of sports performance.

While descriptive statistics, means and differences are used in traditional methods in psychological measurements and applications, linear algebra, probability and developing mathematical and physical components are the most important comparison criteria in artificial intelligence applications.

AI and Conventional Psychological Assessment Tools in Sports

Conventional Assessment Tools

Traditional methods have been used for many years in sports psychology to assess the mental performance of athletes. These methods generally include self-report questionnaires, observational assessments, physiological measurements, and cognitive tests.

Table 10. Conventional Assessment

Evaluation	Method Description
1. Self-Reporting Questionnaires and Scales	**These are structured questionnaires in which athletes assess their own psychological states factors such as motivation, stress, anxiety, and focus.**
Sports Competitive Anxiety Scale (SCAT)	Used to measure athletes' anxiety levels before competition.
Emotional Intelligence Scale	Emotional Intelligence Scale: Measures athletes' emotional awareness and ability to manage their emotions.
Psychological Resilience Scales	Psychological Resilience Scales: Evaluates how athletes perform under pressure (e.g., Sport Mental Toughness Questionnaire - SMTQ).
Focus and Concentration Tests	Focus and Concentration Tests: Tests aimed at measuring the level of attention during performance.
Observational Assessment	**These are assessments conducted by coaches, sports psychologists, and experts. The athletes' behaviors during training and matches are usually examined.**
Body Language and Behavior Analysis	Body Language and Behavior Analysis: The reactions of athletes under pressure, body language in stress situations are observed.
Analysis of Training and Match Videos	Analysis of Training and Match Videos: The decision-making processes of athletes, their attention level and focus capacity during the game are examined.
Coach Feedback	Coach Feedback: Coaches evaluate the mental performance of athletes by long-term observation.
Physiological Measurements	**Evaluation is made by measuring some physiological reactions that are directly related to mental performance.**

Heart Rate (HR) and Heart Rate Variability (HRV)	Heart Rate (HR) and Heart Rate Variability (HRV): Used to determine stress level and mental endurance.
Respiratory Rate Measurements	Respiratory Rate Measurements: Changes in respiration due to the effects of stress and anxiety are evaluated.
Muscle Tension (EMG - Electromyography)	Muscle Tension (EMG - Electromyography): Tension levels are analyzed by measuring muscle activation of athletes under stress.
Breathing Analysis with Biofeedback - Physiological breathing measurements	Breathing Analysis with Biofeedback - Physiological breathing measurements Using biofeedback devices, athletes' breathing, heart rate and other physiological parameters are monitored. Breath control in stressful situations is an important factor that shows mental endurance.

4. Cognitive Performance Tests	**Tests applied to evaluate cognitive skills of athletes such as attention, memory and reaction time.**
Stroop Test	Used to measure cognitive flexibility and attention.
Reaction Time Tests	Reaction Time Tests: Used to measure athletes' fast decision-making and reflex speeds.
Go/No-Go Test	One of the tests used to measure attention and impulse control.
Digital Memory Tests	These are tests that evaluate short- and long-term memory capacity.

5. Tests Based on Visual and Auditory Stimuli	**These are methods used to evaluate athletes' focus levels and reactions to environmental factors**
Eye Tracking Tests	The eye movements of athletes are examined to determine which points they focus on more.
Auditory Reaction Tests	It measures how quickly and accurately athletes respond to auditory commands.

Although traditional methods have been used in sports psychology for many years, they have some limitations. Self-report surveys can be subjective, observational assessments can be based on personal interpretations, and physiological measurements may not always fully reflect mental performance. Therefore, hybrid approaches supported by artificial intelligence and new technologies offer the opportunity to evaluate the mental states of athletes more accurately and objectively.

Artificial Intelligence-Supported Methods in Measuring and Evaluating Mental Performance in Athletes

Artificial intelligence (AI) and machine learning offer new generation methods that allow athletes to analyze their mental performance more objectively, quickly and in detail. These methods, which are used to overcome the shortcomings of

traditional measurement techniques, are supported by big data analysis, biometric measurements, emotion recognition systems and cognitive tests.

Table 11. AI assessment

Evaluation	Method Description
1. Artificial Intelligence-Supported Data Analysis and Pattern Recognition	AI algorithms can analyze large amounts of data and reveal hidden patterns related to athletes' mental performance.
Machine Learning Models (ML);	Support Vector Machines (SVM), Decision Trees, Random Forests, Deep Neural Networks (DNN),
Big Data Analytics:	Analyzing all data collected by athletes during training and matches
Determining factors that indicate a decrease or increase in performance	Artificial intelligence models that predict players' psychological stress levels
2. Biometric and Physiological Data-Based Artificial Intelligence Applications	Mental performance is directly related to physiological reactions. AI can better analyze athletes' psychological states by processing this data.
EEG (Electroencephalography) + Artificial Intelligence;	Determining athletes' focus, stress and motivation levels by analyzing brain wavesAlpha, beta and classification of theta waves by AI Analyzes the effectiveness of meditation and attention-enhancement techniques.
Measurement of Response to Stimulus+ AI;	Analyze and enforcement of the effectiveness of focus and response techniques
Heart Rate Variability (HRV) + AI;	Stress management and mental endurance measurements. Emotional state analysis with autonomic nervous system data
GSR (Galvanic Skin Response) + AI;	Estimating stress levels of athletes by measuring emotional responses, analyzing the effect of stress on in-game performance with machine learning
Eye-Tracking + AI	Determining the attention level and visual focus points of athletes. Measuring reaction time and cognitive workload
Breath Control + AI	Equalize and measuring emotional responses with breath, Analyzing the effect of stress on in-game performance with machine learning
3. Mental State Analysis with Emotion Recognition and NLP (Natural Language Processing)	AI can use techniques such as facial expressions, tone of voice and text analysis to analyze the emotional states of athletes.
Facial Recognition and Emotion Analysis;	Analyzing emotions from athletes' facial expressions with computer vision, Determining signs of stress, motivation and fatigue during training and matches, Determining athletes' motivation levels with NLP techniques
Speech and Voice Analysis;	Detecting athletes' mental states by analyzing voice tone and speed changes

Athlete Diaries and NLP;	Monitoring emotional changes by analyzing athletes' written diaries, Estimating psychological states by performing keyword analysis with NLP
4. Virtual Reality (VR) and Artificial Intelligence-Supported Mental Training	AI can help athletes improve their mental performance with virtual reality environments.
AI-Powered Mental Simulations;	VR simulations that test players' decision-making skills under stress, Personalized VR exercises to increase mental endurance
Neurofeedback Training;	Offering focus and stress management training by analyzing brain waves in real time Feedback systems that allow athletes to learn to control their brain activity
5. In-Game Performance Analysis and Artificial Intelligence-Based Decision Support Systems	AI can help improve decision-making mechanisms by analyzing the mental performance of athletes during the game.
AI-Powered Video Analysis Systems;	Measuring the speed and accuracy of decision-making by analyzing athletes' in-game movements, Predicting the in-game psychological strategies of opposing players
Personalized Mental Training Programs;	Creating mental training plans customized to each athlete's needs Determining training intensity according to athletes' motivation levels

AI-powered methods offer revolutionary innovations in evaluating and improving the mental performance of athletes. It provides significant advantages for coaches and athletes by providing more objective, faster and personalized analyses compared to traditional methods.

Traditional Methods or Artificial Intelligence-Supported Methods

There are significant differences between traditional methods and artificial intelligence-supported methods in measuring and evaluating the mental performance of athletes. If we make the comparison based on three basic criteria:

Table 12. Differences between traditional methods and artificial intelligence-supported methods

Accuracy Rate of Analysis

Criteria	Traditional Methods	Artificial Intelligence Supported Methods
Self-report surveys	There is a risk that athletes may report their emotions incorrectly or biasedly.	It can make objective analysis with NLP and emotion recognition.
Observational evaluation	It can be subjective because it is based on coach and psychologist comments.	AI can detect patterns more accurately with big data analysis.
Cognitive tests	It measures certain variables with standard tests, but it may not always reflect individual differences.	It can analyze individual cognitive performance changes in detail with machine learning.
Physiological measurements	Data such as heart rate and respiratory rate are analyzed manually; there may be a margin of error.	AI can make more precise predictions by instantly processing data such as EEG, HRV and GSR.

Capacity to Provide Rapid Feedback

Criteria	Traditional Methods	AI-Supported Methods
Self-report and questionnaires	Athletes filling out forms and the evaluation process can take time.	It can perform sentiment analysis by collecting instant data.
Observational assessment	Coaches or experts watch and analyze matches and training sessions, it takes time.(Subjective factors)	AI-based video analysis can process data instantly. (Objective factors)
Physiological measures	When data is analyzed manually, the process takes longer.	AI provides instant feedback by performing real-time analysis.

Individualized Reporting and Recommendation

Criteria	Traditional Methods	Artificial Intelligence-Supported Methods
Personalization	Evaluates on general scales and standard tests, individual differences can be ignored.	It can develop special recommendations for each athlete by analyzing personal data.
Recommendation Systems	A coach or psychologist must make manual comments.	AI can recommend the most appropriate training programs with big data analysis.
Development Tracking	Traditional reports are prepared at specific time intervals.	AI provides dynamic performance monitoring by continuously collecting data.

AI-powered systems excel at individualized reporting so as to offer tailored recommendations based on athletes' historical data.

General Evaluation

Criterion	Traditional Methods	Artificial Intelligence Supported Methods
Accuracy	May have subjective error, limited data analysis.	It has a higher accuracy rate with big data analysis.
Feedback Rate	Process may be slow as manual analysis is required.	It provides fast feedback by performing real-time analysis.
Individualization	Uses general scales, limited customization.	It can provide special analysis and suggestions for each athlete.

The following section presents an analysis of studies retrieved from Endnote, ProQuest, and EBSCOhost.

Table 13. Qualitative analysis

Name of the Research	Problem statement	Independent variables	Dependent variables	Research Gap	Methods Used	Practical Implications	Findings
Artificial Intelligence Applications in the Sports Industry	Sports rehabilitation, injury prevention and athlete training management.	Mobile health detection systems are proposed for remote areas.	Explores mobile health solutions for underserved areas.	Artificial Neural Networks (ANN) for sports predictions.	ANN models analyze historical match results, ethical, player statistics, and team performance to forecast future outcomes. Application of statistical pattern classification in sports analytics.	A mobile health detection system for areas with limited medical access, enhancing physical health assessments.	AI in sports rehabilitation shows a 10.4% higher recovery rate compared to traditional methods, indicating improved patient outcomes. The use of AI in training can optimize performance by correcting movement patterns.
Technology Meets Sport Psychology How Technology and Artificial Intelligence Can Shape the Future of Elite Sport Performance	Moravec's paradox highlights challenges in replicating human sensorimotor skills in AI.	The role of sport psychology in interpreting data, and the psychological insights. Data analytics.	Performance analysis.	Effective prediction methods for athlete behaviors in analytics departments.	Quantitative and qualitative research expertise to inform strategic decisions in elite sports. Analyzing to understand broad tendencies and specific athlete behaviors.	Uncertainties in big data analytics can enhance decision-making for coaches and athletes,	Combining big data with idiosyncratic data for effective athlete performance analysis.
Predicting athletic performance from physiological parameters using machine learning: Example of bocce ball	The study aims to classify uses machine learning clustering methods for classification.	Machine learning techniques were applied to predict physiological parameters.	The performance specifically categorized as high-performance bocce players (HPBP)	Focused on a limited sample of national bocce athletes.	V vector machines-radial basis function (SVM-RBF) kernel is utilized for classification.	Machine learning applications can streamline the selection of high-potential bocce athletes, improving decision-making processes.	Dynamic balance and personal records is set at $p < 0.05$. Machines-radial basis function (SVM-RBF) kernel accurately predicted all HPBPs and 75% of LPBPs.

Name of the Research	Problem statement	Independent variables	Dependent variables	Research Gap	Methods Used	Practical Implications	Findings
Neuroassessments in Sports: An Integrative Approach for Performance and Potential Evaluation in Athletes	Traditional assessments focus primarily on physical fitness, neglecting cognitive aspects.	Electrodermal Activity, Heart Rate, Heart Rate Variability) and electrophysiological markers.	Standardized tools for athletic performance selfregulation skills and cognitive control as significant factors .	The assessment procedures for psychological and cognitive factors are a lack of standardized tools.	An Electrodermal and electrophysiological marker utilizes autonomic measures to regulate attention in competitive contexts (efficiency of attention regulation).	Protocols combining cognitive techniques and neuromodulation devices can enhance attention regulation and executive control in sports.	Psychometric, behavioral, and neuroscientific assessment tools to evaluate athletes' performance and self-awareness, self-regulation, and executive control.
Examining Psychometric Properties of The Sport Mental Toughness Questionnaire-SMTQ	Mental toughness in sports performance. The aim is to adapt the Sport Mental Toughness Questionnaire to Turkish.	Emotional regulation and decision-making skills	Adapting a Sport Mental Toughness Questionnaire to Turkish	Lack of Questionnaire.	Exploratory Factor Analysis (EFA) is also utilized to assess the inventory's factor structure. The study analyzes the sub-dimensions of the scale, including "Confidence," "Control," and "Continuity".	Three key dimensions: Trust, Control, and Continuity. Understanding these factors can lead to better strategies for managing stress in high-pressure environments.	Training programs aimed at improving emotional regulation and decision-making skills. The internal consistency of the inventory was assessed using Cronbach Alpha values.
Artificial Intelligence and Machine Learning approaches in sports: Concepts, applications, challenges, and future perspectives	AI and ML applications face challenges in sports dynamics and performance aspects.	Agent-based modeling and systems dynamics for modeling complex sports systems	AI and Machine Learning models applied in sports, focusing on injury prediction and performance analysis.	The need for developing Big Data database.	Techniques such as Artificial Neural Networks, decision tree classifiers, and support vector machines are highlighted. The paper emphasizes modeling complex sports systems.	AI and ML applications. Understanding the multifactorial nature of sports injuries can improve Prevention. The potential of wearables in collecting data and providing real-time feedback	AI can enhance diagnostic accuracy for sports-related injuries. The research identifies the need for model validation in specific contexts to ensure external validity.

Name of the Research	Problem statement	Independent variables	Dependent variables	Research Gap	Methods Used	Practical Implications	Findings
Guidelines for Applying Psychometrics in Sports Science: Transitioning from Traditional Methods to the AI Era	Psychometrics transitions from traditional methods to the artificial intelligence (AI) era.	AI-driven psychometrics	Ethical considerations related to AI-driven psychometrics are examined, focusing on privacy and bias .	Psychometrics, emphasizing the integration of AI Technologies.	Statistical analysis methods, including correlation coefficients, confirm test-retest reliability.	Ai in psychometrics in sports Science is encouraged to employ rigorous methods to ensure objectivity in qualitative data analysis.	A comprehensive framework that aids researchers, coaches, and practitioners in effectively utilizing psychometrics for athlete evaluation and development.
Research on intelligent analysis strategies to improve athletes' psychological Experience in the Era of Artificial Intelligence	The research emphasizes the psychological challenges athletes face when transitioning from relaxed training to high-pressure competition.	Intelligent decision-making system dimensions and attributes: 2-dimensional 5 attributes and 3-dimensional 8 attributes.	Psychological experiences parameters (αand multi-dimensional θ) evaluated using PCCR and Average MSE.	Exploration regarding the long-term effects of the proposed intelligent decision-making system on athletes' psychological well-being.	CEMSHE method for calculating (quantitate) indicators of information related to psychological intelligence. An aggregate normalized information method (ANI) is introduced to process KL information.	The research validates the effectiveness of a multi-dimensional dual-objective strategy through Monte Carlo simulation employs D-optimality to develop a multidimensional version of the DWI method, termed mDWI. .	The findings suggest that the intelligent decision-making system can enhance athletes' psychological training effects the need for a mental toughness scale tailored for athletes in training and competition contexts. The research utilizes a normalization method to standardize data for better analysis.
Development Study of Psychological Performance Evaluation Scale in Sports	Importance of identifying to collect original quantitative data to address focusing on various psychological parameters across different sports disciplines.	The research primarily focuses on the development and psychometric properties assessment of psychological performance in sports and the methodology.	Psychological Performance Assessment	Athletes' performance across different sports disciplines.	The research employed a random sampling method to select 840 active elite athletes from various sports disciplines for the study.	The study utilized Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) to examine the scale's construct validity.	Reliability was assessed using Cronbach's Alpha, which ranged from 0.84 to 0.94, indicating high reliability.

Name of the Research	Problem statement	Independent variables	Dependent variables	Research Gap	Methods Used	Practical Implications	Findings
Current Approach in Athlete Health: Computer Based Psychological Measurement Applications	Laboratory applications in psychological health compared with other disciplines. Understanding emotional processing.	Applying computer-based psychological measurements and suggests potential solutions	Emotions, emotion regulation, and sports performance	Emotion regulation, and sports, as existing studies may not comprehensively address these connections.	Applications in psychological health, highlighting their use as alternatives to traditional methods. .	Pictures of Facial Affect (POFA) and Emotion Recognition Tasks (ERT) are used to assess athletes' emotional states and their influence on performance.	Applicability of tools like Pictures of Facial Affect (POFA) and Emotion Recognition Task (ERT) for measuring emotions and facial recognition.

Theories like Yerkes-Dodson's Law and the Inverted-U Hypothesis help in understanding the role of arousal in performance, while models such as Bandura's Self-Efficacy and Flow Theory explain how mental states can be quantified and improved (Yerkes, Dodson, 1908). These theories offer a framework to develop targeted interventions, guiding coaches and sports psychologists in tailoring training methods to meet individual athlete needs. An important aspect discussed in the paper is the integration of traditional and AI-supported methods to provide a more comprehensive evaluation of mental performance (Crane et al, 2017). While traditional methods give a broad overview through self-report and observational data, AI methods can provide more precise and real-time feedback, which is critical in fast-paced sports environments (Deci, Ryan, 1985). This combination helps in not only diagnosing current mental states but also in predicting future performance trends and preparing athletes to handle competitive pressure effectively.

In summary, the conclusion of the paper stresses that an integrated approach combining conventional psychological assessments with advanced, AI-driven techniques leads to more accurate, objective, and personalized evaluations of athletes' mental performance (Aydoğan, Konaş, 2022). Such advancements promise improved training procedures and enhanced competitive performance through better understanding and management of psychological factors in sports (Deci, Ryan, 1985).

The following recommendations are made in accordance with the advantages and disadvantages of the analyzed articles: risk factor evaluation, structural strength calculations, examination of existing cracks, deformations, and damages, determination of the effects of environmental actors on the structure, simulation of the structure's behavior with computer-aided modeling, testing of the structure's response to various scenarios, and presentation of reinforcement suggestions within a unique, ethical, and moral framework for each individual.

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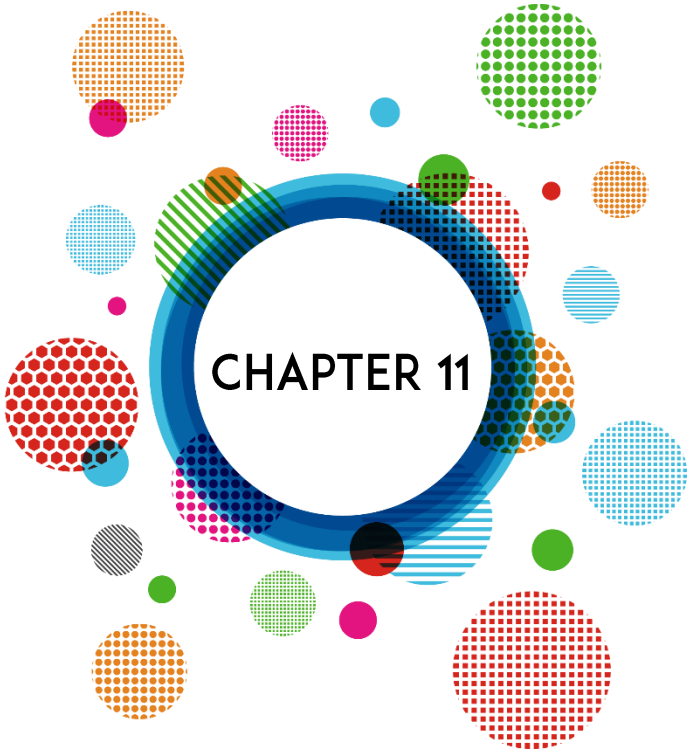

Central Giant Cell Reparative Granuloma

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1. Introduction

The World Health Organization (WHO) defines giant cell reparative granuloma (GCRG) as a benign, localized intraosseous (within the bone) lesion characterized by cell-rich fibrous tissue containing multiple hemorrhagic foci, osteoclast-like multinucleated giant cells, and trabecular bone (Bocchialini et al., 2020). The term "giant cell granuloma" was first introduced by Henry L. Jaffe in 1953 to describe a non-neoplastic, reactive lesion caused by intraosseous hemorrhage, distinguishing it from giant cell tumor (GCT) of bone (Jaffe, 1953; Orhan et al., 2010). In early descriptions, due to its hemorrhagic characteristics, many researchers believed that trauma played a role in its etiology, and therefore the lesion was referred to as a "reparative" granuloma (Angekini et al., 2018).

2. Etiology and Pathogenesis

The etiology of giant cell reparative granuloma (GCRG) is not yet fully understood (Orhan et al., 2010; Richardson, 2022). One prevailing theory suggests that GCRG arises as a localized reactive lesion due to hemorrhage and the subsequent inflammatory response following trauma (Alton et al., 2009; Richardson et al., 2022). However, many cases of GCRG have been reported to occur spontaneously, without any history of trauma (Orhan et al., 2010; Angekini et al., 2019; Arai et al., 2016). An alternative hypothesis proposes that GCRG is a true neoplasm and a counterpart of the giant cell tumor (GCT) typically found in long bones (Triantafillidou et al., 2011; Richardson et al., 2022). Furthermore, several cases have documented recurrence or exacerbation of GCRG during pregnancy, suggesting the lesion may be hormonally responsive (Bataineh).

The role of genetic factors in the etiology of GCRG remains uncertain. Lesions resembling giant cell granulomas have been observed in the jaws of patients with certain genetic syndromes, such as neurofibromatosis type 1 (NF-1), cherubism, and Noonan syndrome. Additionally, chromosomal translocations identified in GCTs of long bones raise the possibility of chromosomal abnormalities contributing to the pathogenesis of GCRG, though this remains a subject of debate (Triantafillidou et al.; O'Connell et al., 2013). De Lange et al. (2007) suggested that the SH3BP2 gene region, or adjacent genes, may contribute to the development of GCRG by influencing osteoclastic activity; however, SH3BP2 mutations have not been detected in children with isolated GCRG (Idowu et al., 2008). Gomes et al. also reported sporadic cases with H3F3A p.Gly34Trp or p.Gly34Leu mutations (Hyckel et al., 2005; Gomes et al., 2014).

3. Epidemiology

Lesions that arise within bone are referred to as central giant cell reparative granulomas (CGCRGs), whereas those occurring in soft tissue regions such as the oral cavity are termed peripheral giant cell reparative granulomas (PGCRGs) (Saadaat et al., 2022; Angekini et al., 2019).

Approximately 43% of CGCRGs are located in the jaw region and account for about 7% of benign jaw masses (O'Connell et al., 2013; Richardson et al., 2022). CGCRGs are observed nearly twice as frequently in the mandible as in the maxilla. Among maxillary lesions, 75% are found in the anterior region, while mandibular lesions are distributed equally between the anterior and posterior regions (de Lange et al., 2004; Orhan et al., 2010). Following the jaw, the temporal bone (33.3%) and paranasal sinuses (11.8%) are the most common sites of occurrence (Richardson et al., 2022). Less commonly, CGCRGs can arise in bones surrounding the orbit and other cranial bones such as the sphenoid and ethmoid (Ustündağ et al., 2002). Additionally, cases involving the hard palate, zygomatic bone, and nasal bone have also been reported in the literature (Maerki et al., 2012; Chrcanovic et al., 2018; Ishinaga et al., 2013).

CGCRG may also occur outside the head and neck region. Beyond this region, the most commonly affected sites (in approximately 40% of cases) are the small bones of the hands and feet. Rare cases involving the femur, tibia, ulna, humerus, vertebrae, clavicle, radius, fibula, ribs, and scapula have also been reported in the literature (Angekini et al., 2019).

Although CGCRG can be seen at any age, 75% of cases are diagnosed before the age of 30 (mean age: 27.5 years) (Bataineh et al., 2002; de Lange et al., 2004; Orhan et al., 2010; Devi et al., 2013). It is rarely seen after the age of 50 (Eisenbud et al., 1998). In males, it is most frequently diagnosed between the ages of 10 and 14, while in females it is most common between 15 and 19 years of age (de Lange et al., 2004).

Overall, females are generally considered to be more prone to developing CGCRG, with some studies reporting a threefold higher incidence in females compared to males (de Lange et al., 2004; Chrcanovic et al., 2018). However, other publications have reported equal distribution between sexes (1:1 male:female) (Bayar & Ak, 2015; Devi et al., 2013).

Multifocal lesions are typically associated with genetic conditions such as cherubism, Noonan syndrome (Edwards et al., 2005), and neurofibromatosis type 1 (NF-1) (Ruggieri et al., 1999), as well as with systemic disorders including fibro-osseous lesions, odontogenic fibroma (Ficarra et al., 1993), brown tumors of

hyperparathyroidism (Cohen, 1998), fibrous dysplasia, and ossifying fibroma (Penfold et al., 1993). Most unifocal lesions are isolated (Ardekian et al., 1999), although sporadic cases of isolated multifocal CGCRG have also been reported in the literature (Orhan et al., 2010).

CGCRG is generally classified into two types based on clinical and radiographic features: aggressive (A-CGCG) and non-aggressive (NA-CGCG) forms (Chuong et al., 1986; Ficarra et al., 1993). Lesions smaller than 5.0 cm, asymptomatic, exhibiting slow growth, not associated with teeth or cortical bone perforation, and with no observed recurrence are considered non-aggressive (NA-CGCG). In contrast, lesions larger than 5.0 cm that present with at least three of the following features—pain, rapid growth, root resorption, displacement of teeth, or cortical bone perforation—and demonstrate recurrence following surgical enucleation/curettage are classified as aggressive (A-CGCG) (Latorre et al., 2024).

Aggressive lesions typically show a more pronounced association with teeth, such as root resorption or tooth displacement (Kruse-Lösler et al., 2006; Peacock et al., 2012). These lesions have a higher likelihood of recurrence. Conversely, non-aggressive lesions tend to grow slowly, may be asymptomatic or minimally symptomatic, and are often not accompanied by significant clinical or radiological findings (Shrestha et al., 2021).

4. Clinical Features and Diagnostic Approach

The presenting symptomatology of CGCRG varies significantly depending on the anatomical location of the tumor. As CGCRGs predominantly develop in the jaw region, the most commonly reported symptom is a painless jaw swelling (de Lange et al., 2004; Stewart, 2012; Chrcanovic et al., 2018). The most frequent clinical manifestations include pain, swelling, and palpable bony lesions. Based on the lesion's location, patients may also present with headache, nausea and vomiting, visual disturbances, and proptosis. Although rare, some patients may exhibit facial asymmetry or pathological fractures (Ustündağ et al., 2002; Angekini et al., 2019).

The lesion may cause symptoms due to mass effect in the surrounding tissue. Because of the cancellous structure and thin cortical layer of the maxilla, lesions in this region tend to expand more rapidly, leading to earlier onset of symptoms compared to the mandible. Maxillary lesions may expand anteriorly and cause symptoms such as diplopia, epiphora, nasal obstruction, and epistaxis (Rawashdeh et al., 2006). Lesions located in the nasal cavity may lead to nasal obstruction and epistaxis; those involving the orbital bones or extending into the orbital region may result in proptosis and epiphora; and those situated in the temporal bone may cause

hearing loss, otalgia, and a sensation of aural fullness (Lei & Cui, 2004; Takata et al., 2013).

Diagnosing CGCRG can be challenging. A biopsy is essential for a definitive diagnosis. However, when head and neck CGCRG (HN-CGCRG) is suspected, imaging studies are typically the first step in the diagnostic evaluation (Richardson et al., 2022).

5. Histological Features

CGCG lesions are histologically characterized by an unencapsulated proliferation of spindle-shaped and polygonal mononuclear cells, the presence of osteoclast-like multinucleated giant cells within a vascular stroma, and foci of hemorrhage with hemosiderin pigmentation (Melo-Muniz et al., 2020).

Although some studies have suggested that aggressive CGCRG subtypes contain a greater number of giant cells, increased mitotic activity, and a higher fractional surface area (Kruse-Lösler et al., 2006), both aggressive and non-aggressive lesions share similar histological patterns (Melo-Muniz et al., 2020).

Despite the apparent prominence of multinucleated giant cells, the primary proliferative cellular components of CGCRG are fibroblasts, myofibroblasts, and inflammatory mononuclear cells (Schütz et al., 2010). Dystrophic calcifications and metaplastic ossifications are also commonly observed, typically located at the periphery of the lesion (de Lange et al., 2004). The histological appearance of CGCRG overlaps significantly with that of brown tumors associated with hyperparathyroidism, cherubism, and aneurysmal bone cysts (Triantafilidou et al., 2011).

Immunohistochemical analysis of CGCG cases has revealed increased expression of CD68 and CD163 regardless of clinical variant (Melo-Muniz et al., 2020). Additionally, elevated expression of vascular markers CD34 and D2-40 has been observed in both aggressive and non-aggressive variants. No significant differences in immunohistochemical marker expression have been found between the two subtypes (Peacock et al., 2012; O'Malley et al., 1997).

6. Radiological Features

Imaging plays a critical role in assessing the extent of CGCRG and in planning surgical treatment accordingly (Richardson et al., 2022).

The internal structure of CGCRG is variable, ranging from completely hypodense (low-density) lesions to more complex patterns with granular bony components. Completely hyperdense (high-density) lesions have not been observed. One of the

characteristic radiographic features of CGCRG is the presence of thin or granular septa projecting at right angles from the lesion's periphery, which can serve as a diagnostic clue (Tahmasbi-Arashlow et al., 2022).

Radiographically, CGCRG exhibits a broad spectrum of appearances—from well-defined, small, unilocular lesions to large, multilocular lesions with poorly defined borders that may invade surrounding tissues and cause cortical expansion and perforation (de Lange et al., 2004). Poorly demarcated and destructive lesions may also be observed. Since non-aggressive CGCRGs are slow-growing, 75% of lesions tend to have well-defined margins (Tahmasbi-Arashlow et al., 2022).

Although multilocular appearance has been reported in approximately 66% of cases in most series, de Lange et al. (2004) found that 85% of their cases were unilocular. Radiographic analysis revealed that 56% of CGCRG lesions had well-defined borders, 30% had poorly defined margins, and 14% were continuous with surrounding structures (Orhan et al., 2010). The size and nature of the bony defect vary depending on lesion aggressiveness. Additionally, radiological imaging may reveal displacement of teeth, root resorption, and cortical bone perforation (Shrestha et al., 2021).

Plain radiographs (e.g., panoramic imaging) are typically the initial choice for evaluating jaw lesions. However, due to image distortion, magnification, and superimposition of anatomical structures, plain radiography carries a higher diagnostic error rate (Tahmasbi). The radiographic appearance of CGCRG on plain films is not pathognomonic and may be confused with other jaw lesions (Orhan et al., 2010). Plain radiography was used in 20.8% of cases (Richardson et al., 2022).

Computed tomography (CT) was the most frequently used diagnostic modality, employed in 91.7% of cases. On CT, CGCRGs appear as well-defined, expansile masses with osteolytic changes and granular bone patterns with internal septations. CT may also show cystic areas, calcifications, and bone remodeling; in some cases, lesions may mimic infected mucoceles or multiloculated cysts (Richardson et al., 2022).

The second most common imaging modality after CT is magnetic resonance imaging (MRI). MRI offers advantages over CT due to its high soft tissue contrast and multiplanar imaging capabilities. Some studies have suggested that MRI may be the most effective imaging tool for evaluating CGCRG. On MRI, CGCRGs typically demonstrate low to intermediate signal intensity on both T1- and T2-weighted images. When fibrosis, osteoid formation, hemorrhage, or hemosiderin deposition is present within the lesion, variable signal intensities may be observed (Richardson et al., 2022; Shrestha et al., 2021).

However, on CT and MRI, CGCRGs may be radiologically indistinguishable from giant cell tumors (GCT), aneurysmal bone cysts (ABC), and brown tumors of hyperparathyroidism (Shrestha et al., 2021).

7. Differential Diagnosis

The differential diagnosis of CGCRG includes true giant cell tumors (GCT), aneurysmal bone cysts (ABC), other giant cell–containing lesions such as chondroblastoma, brown tumors secondary to hyperparathyroidism, fibrous dysplasia (FD), and odontogenic myxomas (Orhan et al., 2010; Tahmasbi-Arashlow et al., 2022).

Differentiating CGCRG from true GCTs is clinically critical due to their differing biological behaviors and treatment approaches, though it can often be difficult and confusing. GCTs are benign yet locally aggressive true neoplasms that typically arise in the epiphyseal regions of long bones, with only about 2% occurring in the skull. In contrast, CGCRGs are more commonly found in the mandible and maxilla. GCTs typically present in the third or fourth decade of life and may undergo malignant transformation (Shrestha et al., 2021). Radiographically, both lesions appear as lytic lesions; however, GCTs may penetrate the cortex, whereas CGCRGs typically do not. GCTs may also present as aggressive, expansile, radiolucent lesions that cause cortical destruction and extend into soft tissue (Angelini). Histological evaluation is essential for accurate differentiation (Orhan et al., 2010). CGCRGs originate from periosteal connective tissue, while GCTs arise from bone marrow stroma (Shrestha et al., 2021). Both lesions consist of multinucleated giant cells and spindle-shaped fibroblasts, but CGCRGs typically contain fewer giant cells, with more osteoid formation, fresh hemorrhage, and hemosiderin deposits. In contrast, GCTs exhibit centrally clustered, evenly distributed nuclei within giant cells, more frequent new bone formation, occasional necrosis, and minimal hemorrhage or fibrosis (Saw et al., 2009; Shrestha et al., 2021).

Aneurysmal bone cysts (ABCs) are non-neoplastic lesions that also contain giant cells and differ microscopically from CGCRG. Histologically, they consist of a sponge-like network of blood-filled spaces lined by fibroblasts and giant cells. Radiographically, ABCs appear as multiple blood-filled cystic cavities within thin walls. On T2-weighted MRI, ABCs demonstrate heterogeneous high signal intensity with fluid-fluid levels, a typical but not pathognomonic feature (Möller et al., 2021; Yu et al., 2014). Unlike CGCRG, ABCs expand rapidly in a balloon-like fashion and most often affect the posterior mandible (Vasconcelos et al., 2013; Bhalodiya et al., 2005; Santos-Briz et al., 2013).

Ameloblastomas are benign tumors of odontogenic epithelial origin with locally aggressive behavior. They are more frequently observed in older individuals (third to fifth decade) and are more common in the posterior mandible compared to CGCRG (Tahmasbi-Arashlow et al., 2022). Radiologically, they often feature thick, undulating internal septa and may appear as dense masses on CT (Shrestha et al., 2021). Histologically, they present with unique features such as hemosiderin pigment, chondroid differentiation, scattered giant cells, and calcifications (Bhalodiya & Singh, 2005).

Brown tumors associated with hyperparathyroidism generally occur at older ages and are characterized by multiple lesions. Their radiographic appearance often mimics CGCRG, making laboratory tests essential for differentiation, including serum parathyroid hormone levels, calcium, phosphate, and alkaline phosphatase (Shrestha et al., 2021; de Lange et al., 2004).

Fibrous dysplasia (FD) is a localized, benign, idiopathic developmental bone disorder characterized by replacement of normal bone with disorganized fibro-osseous tissue. Early FD lesions appear as unilocular or multilocular radiolucent areas that gradually develop radiopaque foci. In the mature stage, the lesion becomes fully radiopaque. Radiographic terms like “ground-glass,” “orange peel,” and “fingerprint” are often used to describe FD (Şekerci et al., 2012; Singer et al., 2004). Histologically, FD consists of spindle-shaped cells within a cellular fibrous stroma interspersed with irregularly shaped immature bone spicules, lacking osteoblastic rimming, suggesting bone formation via metaplasia (Şekerci et al., 2012).

Odontogenic myxoma (OM) is a benign, locally invasive tumor arising from odontogenic mesenchyme (Carvalho et al., 2008). Although slow-growing, it can cause bone destruction, soft tissue infiltration, and tooth displacement (Francisco et al., 2017; Eninaç & Yılmaz, 2023). OMs tend to appear in older patients, are less expansile than CGCRG, and are more frequent in the posterior mandible (Tahmasbi-Arashlow et al., 2022). Radiologically, they vary from unilocular to multilocular radiolucencies, with thin, straight, intersecting septa producing a “tennis racket” or “honeycomb” appearance (Boffano et al., 2017; Albanese et al., 2012; Vasconcelos et al., 2013). On T2-weighted MRI, they show high signal intensity. Histologically, they consist of spindle-shaped cells in a loose, myxoid stroma resembling dental papilla (Eninaç & Yılmaz, 2023).

Hybrid lesions are rare entities that exhibit histological features of two distinct pathologies within a single lesion (Ide et al., 2001). Documented combinations include CGCRG with ameloblastoma, CGCRG with ABC, CGCRG with

odontogenic cysts, and CGCRG with fibro-osseous lesions (Tahmasbi-Arashlow et al., 2022).

8. Treatment

8.1 Surgical Treatment

The traditional treatment for CGCRG is surgical curettage, which is effective in approximately 80% of cases. Other surgical options include peripheral ostectomy, en bloc resection, and reconstruction of the bony defect using autologous iliac crest bone grafts or osseointegrated implants. In aggressive lesions, to prevent recurrence, it is recommended that the lesion be excised along with a 0.5 cm margin of healthy surrounding tissue (Bataineh et al., 2002). In some cases, adjunctive techniques such as laser application or cryoprobe treatment to the lesion margins have also been utilized (Orhan et al., 2010).

Surgical treatment is particularly appropriate for painful, rapidly growing lesions larger than 3 cm (O'Connell et al., 2013).CGCRG is a highly vascular lesion, and significant intraoperative bleeding may occur, potentially requiring blood transfusion (Eisenbud et al., 1988). Additionally, during procedures such as en bloc resection and peripheral ostectomy, complications including root damage leading to tooth loss, facial deformity, and nerve injury may arise (Orhan et al., 2010; O'Connell et al., 2013).

Due to these potential complications, non-surgical medical therapies are recommended particularly for non-aggressive, slow-growing lesions smaller than 3 cm (O'Connell et al., 2013).

8.2 Medical Treatment

Although surgery remains the most common and effective treatment for CGCRG, medical therapies are increasingly being used either as an adjunct or, in some cases, as a primary treatment. The aim of medical therapy is to reduce lesion size in large or aggressive cases to minimize surgical morbidity and prevent recurrence (Camarini & Tolentino, 2022). In addition, medical treatments may serve as the primary modality in patients with contraindications to surgery or in pediatric and adolescent patients where surgery might pose aesthetic concerns (de Lange et al., 2004; Camarini & Tolentino, 2022).

Reported non-surgical treatment options include calcitonin, corticosteroids, interferon, imatinib, and denosumab (Camarini & Tolentino, 2022).

Calcitonin

Calcitonin, a hormone produced by the C-cells of the thyroid, inhibits osteoclastic bone resorption, promotes osteoblastic activity, and lowers serum calcium levels. It has been used in the treatment of bone resorption–related diseases such as osteoporosis (Xie et al., 2020). Calcitonin was first used in CGCRG treatment by Harris in 1993, who proposed it as an alternative to surgery particularly in young patients and those with advanced/aggressive lesions (Borges et al., 2008).

As one of CGCRG's key features is osteoclastic bone resorption, calcitonin has a potential antagonistic effect. Immunohistochemical studies show that the giant cells in CGCRG behave similarly to osteoclasts and express calcitonin receptors on their membranes. Binding of calcitonin to these receptors causes structural changes and inhibits DNA synthesis in the cells (Camarini & Tolentino, 2022; Vered et al., 2006; Corrêa et al., 2024). Though its exact mechanism remains unclear, it is considered to exert an inhibitory effect on bone resorption (Pogrel, 2003).

Calcitonin can be administered as synthetic human or salmon calcitonin, either via subcutaneous injection or as a nasal spray. Salmon calcitonin is preferred due to availability and perceived higher potency (Schreuder et al., 2017).

Dosing regimens include 100 IU/day subcutaneously for 6–12 months, or 200 IU/day intranasally for 6–28 months (Borges et al., 2008; Camarini & Tolentino, 2022).

Studies have reported a lower recurrence rate with calcitonin compared to curettage in aggressive CGCRG cases (9.1% with calcitonin vs. 53.8% with curettage). It has also been used postoperatively to prevent recurrence. Reported side effects include nausea, headache, flushing, diarrhea, and epistaxis (Camarini & Tolentino, 2022). Major disadvantages include the long treatment duration and high cost.

Corticosteroids

Steroid therapy for CGCRG was first introduced by Jacoway et al. in 1988 and has since been supported by multiple studies (Kermer et al., 1994; Terry & Jacoway, 1996; Comert et al., 2006). The proposed mechanisms of action include inducing apoptosis of osteoclast-like cells, inhibiting lysosomal protease release, suppressing transcription factors for cell proliferation, and exerting antiangiogenic effects on endothelial cells (Flanagan et al., 1988; Pharoah et al., 1986; Kermer et al., 1994; Dempster et al., 1997; Camarini & Tolentino, 2022). However, the exact mechanism remains unclear (O'Connell et al., 2013).

The most commonly used corticosteroid is triamcinolone acetonide. Typically, 40 mg is administered intralesionally once or twice weekly for six weeks (Batista-Severo et al., 2018; Osterne). Although lesion shrinkage is usually achieved, complete remission is rare (Camarini & Tolentino, 2022).

While few adverse effects have been reported with short-term use, prolonged corticosteroid use carries risks including osteoporosis, pathological fractures, avascular necrosis, systemic infections, and peptic ulcer disease. Advantages include low cost and shorter treatment duration (Camarini & Tolentino, 2022; Corrêa et al., 2024).

Interferon

Interferon (IFN) has also been explored as an alternative pharmacological treatment in CGCRG (Corrêa et al., 2024). IFN is a cytokine with immunomodulatory, antiviral, and antiangiogenic effects. Studies from the 1980s demonstrated that IFN-alpha-2a inhibits angiogenesis (Sidky & Borden, 1987), leading to its use in treating hemangiomas and malignancies (Schütz et al., 2010; Camarini & Tolentino, 2022).

Given CGCRG's vascular nature, antiangiogenic therapies like IFN-alpha may inhibit giant cell growth and activity (Kaban et al., 1999; Triantafillidou et al., 2011). IFN-alpha-2a is generally used in large lesions as an adjuvant to suppress rapid growth, or postoperatively within 48–72 hours after conservative excision when en bloc resection is not performed. However, interferon monotherapy is insufficient for complete resolution, possibly due to its limited effect on fibrogenic tumor cells (Schreuder et al., 2017; de Lange et al., 2004; Kaban et al., 2002).

Dosing includes $3–6 \times 10^6$ IU/day subcutaneously for 6–12 months (Kaban et al., 2002). Side effects include fever, flu-like symptoms, nausea, lethargy, postnasal drip, rash, alopecia, neutropenia, thrombocytopenia, elevated liver enzymes, spastic diplegia, hypothyroidism, depression, drug-induced lupus erythematosus, and pancreatitis (O'Connell et al., 2013; Camarini & Tolentino, 2022).

Imatinib

Imatinib is an alternative therapeutic option that has been used in the treatment of CGCRG (de Lange et al., 2009). It is a tyrosine kinase inhibitor widely used in the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors (Druker et al., 1996). Imatinib has been shown to inhibit osteoclastic activity and is considered effective in skeletal diseases characterized by excessive osteoclast activation, such as CGCRG (de Lange et al., 2004). Imatinib may be used both as a neoadjuvant and as an adjuvant following surgery.

In reported cases, it has been administered at a dose of 400 mg/day for a duration of 8–9 months (de Lange et al., 2009; Tallet et al., 2023).

Denosumab

Denosumab is a monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL). RANK, located on the surface of osteoclast precursors, initiates osteoclastic differentiation and bone resorption upon binding with RANKL. Denosumab inhibits this RANK–RANKL interaction, thereby halting the osteolytic process (Thomas et al., 2010; Bredell et al., 2018; Polyzos et al., 2019). Due to this mechanism, it is widely used in the treatment of metabolic bone diseases (Polyzos et al., 2019).

CGCRG is characterized by giant cells of osteoclastic lineage, often resulting from RANKL overexpression. Therefore, denosumab is a rational treatment choice for CGCRG (Latorre et al., 2024). Its use has been associated with reduced lesion size, pain relief, and stabilization of the affected bone (Vanderniet et al., 2022).

Denosumab is preferred in cases where surgery is contraindicated or undesirable, especially in pediatric patients, and is also used as an adjuvant in resistant or aggressive lesions (Latorre et al., 2024).

In adults with CGCRG, the recommended denosumab dosage is 120 mg subcutaneously on days 1, 8, and 15 of the first month, followed by monthly injections starting from month 2 (Thomas et al., 2010; Camarini & Tolentino, 2022). Pediatric dosages are generally 70 mg for patients under 50 kg and 60 mg for those under 45 kg, with adjustments based on individual physiology. The treatment duration varies between 1 and 25 months, with a median of 12 months (Latorre et al., 2024).

Adverse effects may occur during or after treatment and are reported in approximately half of all patients. The most common are hypocalcemia during treatment and rebound hypercalcemia after discontinuation. Other reported effects include osteonecrosis, elevated serum urea and creatinine, paresthesia, anemia, hypophosphatemia, myalgia, dizziness, and delayed wound healing (Corrêa et al., 2024). These effects tend to be more frequent in children and adolescents due to higher bone turnover rates (Latorre et al., 2024).

Due to its relatively short half-life (26 days), the skeletal effects of denosumab reverse quickly. As such, rebound hypercalcemia may develop upon cessation, even if hypocalcemia occurs during treatment (Latorre et al., 2024). To prevent hypocalcemia, concurrent oral supplementation with 500–1000 mg calcium and 400–800 IU vitamin D daily is recommended, and serum calcium should be

maintained within the range of 8.4–10.3 mg/dL (de Lange et al., 2004; Higgins et al., 2011).

To prevent post-treatment hypercalcemia, tapering of denosumab dosage and extending the injection intervals is advised. Protocols include reducing the dose by 50% every 3 months for a year or alternating denosumab and zoledronate every 6 weeks for 30 weeks, followed by administration every 12 weeks for 2 years (Hameed et al., 2019; Vanderniet et al., 2022).

Given its high cost and potential adverse effects, denosumab is generally reserved as a last-line pharmacologic option for patients who do not respond to other treatments or do not achieve remission (Latorre et al., 2024).

Among pharmacologic treatments for CGCRG, intralesional corticosteroid injections (triamcinolone acetonide) remain the first-line choice due to their low cost and favorable safety profile. Calcitonin is second-line, followed by IFN-α and imatinib, which are considered third-line options because of their side effects (Latorre et al., 2024).

In adults for whom surgery is contraindicated, in pediatric patients, and in cases of resistance or aggressive disease, denosumab is preferred (Latorre et al., 2024). For high-risk or non-surgical cases, combination therapy can also be applied, including intralesional corticosteroids + subcutaneous interferon and/or calcitonin + oral imatinib (Camarini & Tolentino, 2022).

8. Recurrence and Follow-up

Recurrence rates following treatment of CGCRG have been reported to range between 11% and 49% (Triantafillidou et al., 2011). Recurrence is more common in aggressive lesions, particularly those that perforate the cortical plate and invade adjacent soft tissues (Minic & Stajcic, 1996).

Chuong et al. and Ficarra et al. reported recurrence rates of 72% for clinically aggressive lesions and 3% for non-aggressive lesions (Chuong et al., 1986; Ficarra et al., 1993).

Whitaker & Waldron (1993) documented a recurrence rate of 46.1% for aggressive lesions and noted that the average time to recurrence was approximately 21 months. Recurrence beyond two years is rare; however, a case of recurrence 22 years post-treatment has been documented (Horner, 1989).

Patient age and sex have been identified as potential factors influencing recurrence. Recurrence is reported to be more frequent in males and in the pediatric

population (Triantafillidou et al., 2011), whereas in females, age does not appear to significantly affect recurrence risk (de Lange et al., 2004).

Lesions larger than 3 cm are associated with a higher risk of recurrence (Whitaker & Waldron, 1993). Although de Lange et al. (2004) found no significant difference in recurrence rates between maxillary and mandibular lesions, other studies report a higher recurrence rate in the maxilla compared to the mandible (28.6% vs. 23.2%). This difference may be attributed to the greater technical difficulty of performing surgical curettage in the maxilla (de Lange et al., 2004).

Regular follow-up with CT and MRI imaging is essential for monitoring recurrence after surgical treatment of CGCRG (Shrestha et al., 2021).

9. Conclusion

CGCRGs are most commonly localized in the maxilla and mandible; however, lesions may also occur in the orbit, paranasal sinuses, skull base, and cranial bones such as the temporal, sphenoid, and ethmoid, as well as in the small bones of the hands and feet.

For aggressive lesions—those that grow rapidly, exceed 5 cm in size, cause pain and paresthesia, and are associated with root resorption and cortical perforation—surgical intervention remains the treatment of choice. In contrast, for non-aggressive lesions that grow slowly, are often asymptomatic, and do not cause cortical perforation or root resorption, non-surgical alternatives should be considered.

The traditional treatment for CGCRG is surgical curettage, which is effective in approximately 80% of cases. Medical therapies are employed particularly in large lesions to reduce lesion size, minimize surgical morbidity, prevent recurrence in aggressive forms, and provide a primary treatment option for patients with comorbidities or in pediatric and adolescent populations where surgery may result in cosmetic or functional complications (Camarini & Tolentino, 2022; Corrêa et al., 2024).

Recurrence following CGCRG treatment is possible, and therefore, patients should undergo regular follow-up with interval CT or MRI imaging post-treatment to monitor for recurrence (Camarini & Tolentino, 2022; Corrêa et al., 2024).

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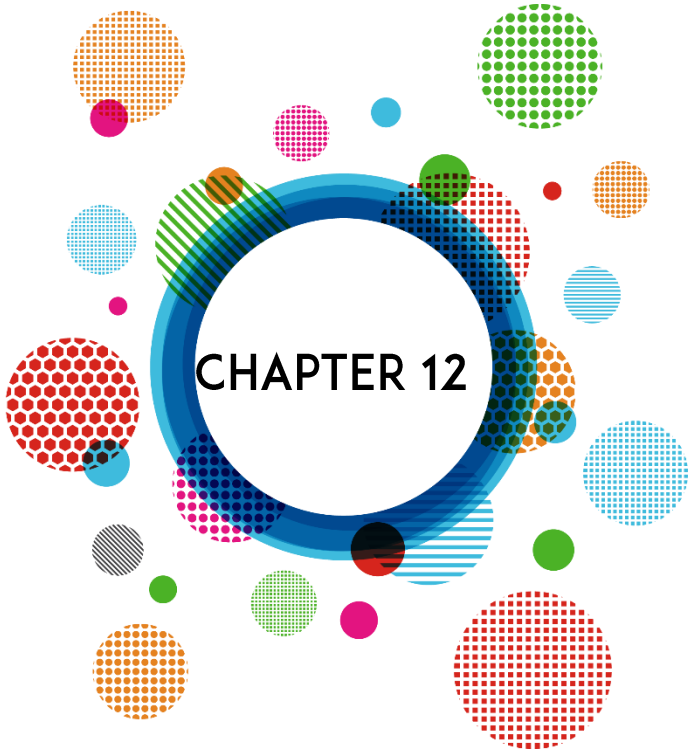

Neonatal Asymmetric Crying Face (NACF)

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Neonatal Asymmetric Crying Face (NACF)

Facial paralysis was defined by Bonar in 1929, and the causes are obstetric or non-obstetric. This definition is still valid today. Regardless of its etiology, facial paralysis refers to the loss of function in the muscles of a part of the face as a result of damage to the seventh cranial nerve. This loss of function can manifest itself in different areas of the face depending on the location and severity of the damage(BONAR & OWENS, 1929).

However, neonatal asymmetric crying face (NCAF) is not a type of facial paralysis. It is a different diagnosis originating from the hypoplasia of the depressor anguli oris muscle first described by Hoefnagel and Penry in 1960(Hoefnagel & Penry, 1960).

In their study, they observed that no asymmetry was observed on the face of a baby at rest, but that one side of his mouth went down while the other remained mobile during crying. With the hypothesis that the mobile side was normal, the mandibular nerve on the mobile side was temporarily blocked and the asymmetry was observed to disappear. However, they could not fully explain the reason for this difference(Hoefnagel & Penry, 1960).

Later, Pape and Pickering reported that the condition originated from the mandibular nerve (Pape & Pickering, 1972), but Nelson and Eng showed in their electrodiagnostic study that there was no mandibular nerve damage but depressor anguli oris hypoplasia (Nelson & Eng, 1972). In subsequent studies, ultrasound imaging revealed cases in which the relevant muscle body showed typical development but failed to function in some individuals(Lahat, Heyman, Barkay, & Goldberg, 2000; Sapin, Miller, & Bass, 2005).

Although it does not carry a serious functional limitation on its own, it has been reported that the presence of NCAF can be seen together with various conditions such as cardiac anomalies, trisomy 18, neuroblastoma, neurofibromatosis type 1, mediastinal teratoma, “collodion” skin disease (CAYLER, 1967; Michalska, Połatyńska, Kępczyński, & Szczukocki, 2019; Nelson & Eng, 1972; Pape & Pickering, 1972; Sapin et al., 2005).

In the case reported by Thomas et al., when the asymmetry revealed by smiling and loud speech in an 80-year-old individual without any stroke or facial paralysis was examined, atrophy was detected in the depressor anguli oris muscle without facial nerve damage. In the advanced scan, the presence of a patent foramen was seen and it was reported that the diagnosis of NCAF should be considered as a differential, especially for heart and kidney scans(Thomas, Morgant, Nambot, Thauvin-Robinet, & Giroud, 2023).

When publications regarding the prognosis of this condition are examined, cases showing spontaneous recovery as well as cases showing no recovery in long-term follow-up have been reported(Kumari, Bhargava, Choudhury, & Ghosh, 1980; Toelle & Boltshauser, 2001; Voudris, Skardoutsou, & Vagiakou, 2003).

When the literature on the management of the process is examined, it is reported that only follow-up may be sufficient, especially in NCAFs caused by trauma, while it is recommended that symmetry be achieved by selective rhizotomy of the contralateral muscles or botox applications as surgical options(Isken, Gunlemez, Kara, Izmirli, & Gercek, 2009; Sabrine, Rejeb, Zitouni, & Zairi, 2020). On the other hand, it has been reported by Sönmez et al. that electrical stimulation used on the affected side may contribute to functional recovery(Sönmez, Güder, Tekin, & Arslan, 2021).

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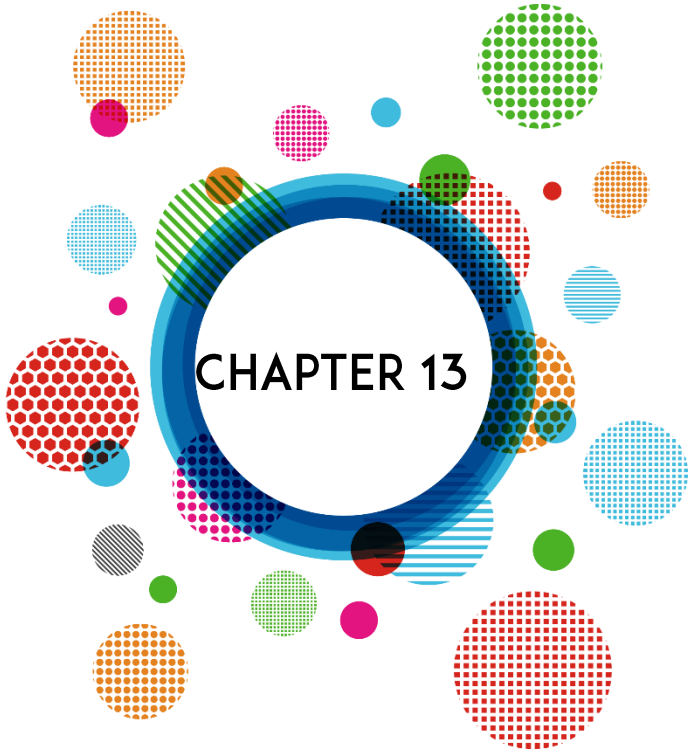

Postoperative Physiotherapy and Rehabilitation in Intracranial Masses

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INTRODUCTION

Although intracranial masses are less prevalent than other types of tumour, they are receiving increasing attention in oncological rehabilitation due to the neurological symptoms they cause. Intracranial masses generally have a high mortality rate and poor prognosis. Benign tumours are difficult to treat completely and have a high recurrence rate (1).

Technological developments have led to the creation of diagnostic and therapeutic methods related to intracranial masses. Chemotherapy, radiotherapy and surgical interventions are employed for diagnosis and treatment. The most appropriate method is determined according to the tumour's characteristics, location and the patient's condition and preferences (2). Despite the development of these methods, the treatments have many side effects. For example, radiotherapy can cause fatigue and encephalopathy while chemotherapy can cause fatigue, pain, nausea and vomiting (3).

The neurological symptoms caused by intracranial masses can vary depending on the tumour's pathology and the lesion's location. Early-stage neurological complications include cognitive dysfunction (80%), motor dysfunction (78%), visual perceptual impairment (53%), sensory problems (38%), and bladder-bowel dysfunction (37%).

The most common neurological and physical complications of brain tumours are: These include cognitive dysfunction, memory impairment, communication problems, mood disorders (such as depression and anxiety), behavioural and personality problems, seizures, pain, headaches, neuropathic pain, muscle weakness, spasticity, dyskinesia, dystonia, fatigue, sensory problems and proprioception disorder, visual and hearing impairment, dysarthria, dysphagia, aphasia, bladder and bowel problems, sexual dysfunction, haemodynamic and vascular complications, hypertension, arterial thrombotic events, deep vein thrombosis, pulmonary embolism, vasogenic oedema, amenorrhoea and infections.

Individualised and multidisciplinary rehabilitation interventions are required to prevent and treat these complications (1). Rehabilitation is essential for more than 80% of individuals with intracranial masses (5).

This chapter synthesises the disorders that may occur after surgery for an intracranial mass and covers acute-period physiotherapy and rehabilitation evaluations and approaches as well as providing evidence-based recommendations.

The aim of surgery for intracranial masses is to remove tumour tissue while causing the least possible damage to the surrounding brain tissue (1). The symptoms frequently encountered after surgery in individuals with intracranial masses are described under the relevant subheadings.

1) MOTOR DISORDERS

Motor dysfunction in individuals with intracranial masses may occur for various reasons, including tumour location, neurosurgery, chemotherapy, radiation therapy and the side effects of steroids or other drugs (6).

Motor dysfunction syndromes differ according to tumour location. Frontal lobe involvement may lead to behavioural and personality problems, apraxia and emotional instability. Parietal lobe tumours may cause neglect, spatial disorientation, apraxia, visual impairment, contralateral proprioceptive agnosia and other sensory disturbances. Temporal lobe involvement may cause disturbances to visual fields, memory, cognition and behaviour. Occipital lobe involvement includes various visual disturbances. Suprasellar tumours in the pituitary region may cause visual field disorders, such as bitemporal hemianopsia. Tumours in the supra-posterolateral part of the thalamus cause astasia, meaning an inability to stand without marked sensory loss. This leads to a tendency to fall to the side opposite the lesion or backwards (7).

Basal ganglia tumours may cause apathy, abulia, hemiparesis, dystonia and cognitive impairment.

Brain stem tumours may cause ataxia, a disorder of coordination, weakness and sensory loss. Involvement of cranial nerve nuclei may result in diplopia, imbalance, dysphagia and other symptoms relating to the specific cranial nerve affected. Cerebellar tumours may cause ipsilateral or midline ataxia, coordination disorders, dysmetria and dysarthria, as well as cognitive and emotional symptoms (8).

Motor deficits affect quality of life and functional independence. They may lead to complications including falls, injuries, venous thromboembolism, pneumonia, skin ulcers, joint contractures and increased mortality (6).

2) INCREASED INTRACRANIAL PRESSURE

Increased intracranial pressure is one of the most common problems encountered in individuals with intracranial masses. Causes include haemorrhage and cerebral oedema. Increased intracranial pressure is characterised by symptoms such as nausea, vomiting, hemiparesis and Cushing's syndrome (hypertension, respiratory irregularity and bradycardia). The main goal in caring for patients is to maintain cerebral perfusion pressure above 60 mmHg and intracranial pressure below 22 mmHg. Although intraventricular pressure monitoring is the gold standard, non-invasive methods such as symptom monitoring, transcranial Doppler and brain tissue partial oxygen pressure are also used. Elevating the patient's head by 30 degrees, maintaining normothermia, and preventing hyperglycaemia are effective in preventing increased intracranial pressure (9).

3) SEIZURES

Seizures are reported in 20–40% of patients with high-grade tumours, 50–85% of patients with low-grade tumours, and 15–20% of patients with brain metastases (10). In certain subgroups of patients with high-grade glioma, seizures indicate disease progression (11). Effective seizure management requires monitoring of tumour growth, brain oedema, intracranial pressure, metabolic issues and other tumour-related factors (12). Surgical resection provided relief from seizures in most patients during the 6-12 month follow-up periods. Temporal lobe involvement and cortical location increase seizure occurrence, while larger tumour size, parietal lobe involvement and increasing age decrease seizure occurrence (11).

4) HEADACHE

Headaches have been reported in 53% of patients with brain tumours. 77% of these patients experience tension-type headaches, which are the most common type of headache. Local traction on pain-sensitive tissues, such as cranial nerves, venous sinuses, arteries and parts of the dura, has been suggested as a possible trigger for headaches.

Headaches can interfere with rehabilitation and reduce motivation. Therefore it needs to be treated. Typically, analgesics are required following craniotomy. Corticosteroids (especially in cases of increased intracranial pressure), surgical procedures and radiation therapy may be employed in the management of headaches (13).

5) DYSPHAGIA

The lifetime prevalence of dysphagia in patients with brain tumours has been reported as 85% (14). Dysphagia may result from focal neurological deficits but is more commonly caused by impaired consciousness (15). Inability to swallow can affect nutrition, hydration and medical treatment. Although no systematic research has been conducted on the effects of hydration and tube feeding in patients with brain tumours, one study reported that swallowing function improved with swallowing therapy and chemoradiotherapy in most patients with supratentorial and infratentorial tumours (16).

6) VENOUS THROMBOEMBOLISM (VTE)

Venous thromboembolism is the most common complication of immobilisation. It is a serious condition frequently observed in individuals with intracranial masses, causing re-hospitalisation and death. The risk of VTE is particularly high in patients with benign tumours, high-grade oligodendroglioma, high-grade glioma and lymphoma, as well as after craniotomies for metastatic or mixed pathology lesions. VTE is one of the main causes of unplanned rehospitalisation in patients with brain tumours. Rehospitalisation rates for VTE vary between 19.7% and 22% (17).

Patients who are readmitted within 30 days of craniotomy for reasons such as VTE are twice as likely to die as those who are not readmitted. Immobility and preoperative motor deficits also increase the risk of VTE. Studies have shown that early post-craniotomy mobilisation therapies, together with mechanical and pharmacological prophylaxis, reduce VTE complications (18). Evidence-based VTE prophylaxis in accordance with American College of Chest Physicians (ACCP) guidelines during inpatient rehabilitation has been shown to reduce the incidence of VTE sixfold in at-risk patients (19).

7) FATIGUE

Fatigue is commonly experienced by individuals with intracranial masses and its prevalence increases with treatment, including chemotherapy, radiotherapy and the use of anticonvulsant drugs (20). Fatigue is the most common side effect of chemotherapy (21). The prevalence of tumour-related fatigue in patients varies from 25 to 99% (22). Light-to-moderate-intensity walking and resistance training are effective treatments for fatigue in individuals with intracranial masses (23). Fatigue can be treated both pharmacologically and non-pharmacologically. Non-pharmacological treatments include various strategies such as physical exercise, yoga, behaviour management, coping strategies, adequate hydration, dietary changes and anaemia management (20, 22).

8) COGNITIVE AND PSYCHOLOGICAL DISORDERS

A) COGNITIVE DYSFUNCTION

Tumours located in the frontal and temporal lobes can cause cognitive dysfunction and distraction. This decreases the speed of information processing. These impairments may worsen with chemotherapy and radiotherapy. This has a negative effect on the rehabilitation process.

Cognitive changes after chemotherapy are primarily related to elevated cytokine levels, DNA damage and neurotoxic damage to white matter. Fatigue, depression and psychosomatic effects may also play a secondary role in cognitive dysfunction (24).

It has been reported that 50–90% of brain tumour patients who survive for more than six months after radiation therapy experience radiation-induced cognitive dysfunction. Radiation-induced encephalopathy may occur in the acute or late phase and it is associated with nerve cell and vascular endothelial cell injury (25).

B) MENTAL STATE CHANGES

In individuals with intracranial masses, 42% of patients have major depressive disorder which may worsen over time. Depression is associated with cognitive dysfunction and functional impairment which decreases quality of life (26).

There is limited data on the effectiveness of combining psychosocial interventions with other treatments such as cognitive and physical therapies for treating mood changes (27).

C) SLEEP DISORDER

Sleep disturbance is a common problem in individuals with intracranial masses and may lead to other symptoms and psychopathology. There are many physical and psychological causes of sleep disturbance such as patient age, tumour size, anxiety, hiccups due to impaired modular stimulation and increased cytokine levels.

A study of 424 patients with intracranial masses found that 19% had moderate to severe sleep disturbance. The findings showed that sleep disturbance was associated with younger age, poor Karnofsky Performance Status, current steroid use and tumour progression on MR imaging. 72% of patients reported fatigue, 59% reported drowsiness and 56% reported distress. Additionally, a higher frequency of moderate-to-severe anxiety and depression was reported compared to individuals without sleep disorders.

Good sleep hygiene and controlling physiological causes such as anaemia and a high-protein diet can reduce sleep disorder symptoms. The American Brain Tumor Association (ABTA) recommends controlling physical causes (such as anaemia and vitamin B12 deficiency), using cognitive behavioural methods and establishing exercise programmes to control fatigue and sleep (29).

9) EFFECTS OF CORTICOSTEROID USE

Corticosteroids have been used for many years to treat tumour-related oedema and associated symptoms. They have been shown to effectively reduce tumour-related pain, nausea and vomiting as well as improving appetite in patients with tumours.

In neuro-oncology, dexamethasone is usually the steroid of choice because of its long half-life, low mineralocorticoid effect and reduced likelihood of causing psychosis. Around 70% of patients with brain tumours report improvement in symptoms while taking steroids. Steroids are also administered before elective surgery to improve clinical outcomes by reducing postoperative oedema.

However, corticosteroid use can have adverse effects, including glucose intolerance, colour changes, immunosuppression, hypertension, electrolyte disturbances, gastrointestinal bleeding, osteoporosis and avascular necrosis. As most of these side effects are dose-dependent, it is important that patients receive the lowest effective dose possible (30).

10) ANTIDIURETIC HORMONE RELEASE SYNDROME

Antidiuretic hormone release syndrome has been observed in patients with primary brain tumours, resulting in hyponatraemia which may manifest as headache, vomiting, delirium, seizures and coma. This syndrome causes a fluid and electrolyte imbalance in patients. Failure to control the syndrome can lead to intracranial arterial stenosis (ICAS), respiratory arrest and death. These patients should be administered hypertonic fluid treatment and monitored for signs of hyponatraemia (31).

IMPORTANCE OF POST-OPERATIVE ACUTE PERIOD PHYSIOTHERAPY AND REHABILITATION

Patients with intracranial masses often experience neurological impairment resulting in functional deficits. Medical complications in these patients include venous thromboembolic disease, inappropriate antidiuretic hormone syndrome, dysphagia and seizures. Psychological symptoms, including depression, fatigue and changes in mood and personality, may be associated with other symptoms such as headaches, sleep disorders and cognitive impairment (32). To manage these symptoms, a personalised rehabilitation programme is required alongside various treatments. Rehabilitation interventions focus on preventing and improving these complications, thus protecting and improving quality of life (6). A multidisciplinary team approach and open communication with patients and their families are essential for successful rehabilitation (1).

OBJECTIVES OF POSTOPERATIVE ACUTE PERIOD PHYSIOTHERAPY AND REHABILITATION

Thanks to technological advances in surgery, chemotherapy and radiotherapy, the survival rate in individuals with intracranial masses has increased significantly. This has created an increasing need to address potential complications and restore quality of life (33).

Most individuals with intracranial masses are referred for rehabilitation following neurosurgery to address motor, psychological and cognitive disorders. Motor dysfunction can lead to impaired mobility and activities of daily living, as well as pain, anxiety, depression, loss of functional independence and a decreased quality of life. Rehabilitation targets the causes of motor dysfunction and its impact on physical function, well-being and quality of life (6). Although still controversial, studies have shown that rehabilitation improves quality of life (34).

A rehabilitation care plan should be developed for all primary brain tumour patients, regardless of their condition. This plan should clearly define the patient's disorders, disabilities and strengths, as well as their short- and long-term functional goals and the treatment strategies that can be employed to achieve these goals and prevent potential complications (35).

The goals of rehabilitation for individuals with intracranial masses are to prevent secondary complications, reduce neurological disorders and teach compensatory strategies for remaining disorders. The type and location of the tumour and the time elapsed since diagnosis, are important factors in determining these goals (36).

POSTOPERATIVE ACUTE PERIOD PHYSIOTHERAPY AND REHABILITATION EVALUATIONS

The most significant causes of disability in individuals with intracranial masses are motor impairments and muscular coordination disorders. These issues impact activities of daily living, creating psychological and social burdens for patients, their families, carers and society. They also have a negative effect on functional independence and quality of life.

Using clinical outcome assessments with these patients gives us a general idea of their condition (37).

- Methods used to assess motor function:

  Berg Balance Scale

  Box and Block Test

  Modified Ashworth Scale

  Motor Assessment Scale

  Canadian Neurological Scale

  Fugl-Meyer Assessment

  Manual Function Test

  Medical Research Council Muscle Strength Rating

  Posture Assessment Scale for Stroke Patients

  Standing balance

  Sitting balance

  10-metre walking test

- Methods used to assess performance:

  Eastern Cooperative Oncology Group Performance Status (ECOG)

  Karnofsky Performance Status (KPS).

- Methods used to assess gait:

  Functional Gait Categories:

Hauser Index

- Methods used to assess functionality:

  Functional Independence Measure (FIM):

  - Korean version of the Barthel Index (38).

POSTOPERATIVE ACUTE PERIOD PHYSIOTHERAPY AND REHABILITATION APPROACHES

Rehabilitation interventions for individuals with intracranial masses should begin as soon as the patient is stabilised and there are no longer any life-threatening issues.

During the acute care phase, it is crucial to prevent medical complications and regulate and manage general health functions such as nutrition, adequate fluid intake, bowel and bladder function, sleep and body balance. Early mobilisation should also be encouraged, as should efforts to regain self-care activities (35).

Early mobilisation in individuals with intracranial masses helps to prevent complications of immobilisation, including venous thromboembolism, contracture development, constipation, orthostatic hypotension, and pneumonia. It promotes early walking and the development of activities of daily living. Restoring self-care activities increases strength, endurance, awareness, communication, problem-solving skills and social activity (35).

Rehabilitation protocols usually include physical therapy, occupational therapy, psychological support and cognitive therapies. When rehabilitating individuals with tumours, attention should be paid to communication with patients and their families and to the palliative care process. Physiotherapists should aim to eliminate existing disorders, prevent complications and improve quality of life by providing a physiotherapy and rehabilitation programme that is appropriate for the patient's functional level and psychosocial status (22, 28).

EXERCISE

Exercise improves aerobic capacity, body composition and levels of physical activity in individuals with an intracranial mass (13). Therapeutic exercise can stabilise painful areas and improve myofascial pain (22).

A study conducted during hospitalisation after surgery in individuals with intracranial masses reported that an intensive rehabilitation programme consisting of exercises to improve range of motion, graded resistance training, balance training, endurance training and gait training improved motor and cognitive function.

Another study reported that a 90-minute programme consisting of a warm-up, cardio and strength training, and body awareness training, all tailored to individual needs and performed three times a week, improved patients' emotional function,

reduced fatigue and uncertainty about the future, and increased muscle strength and reduced the time taken to complete the 10-metre walk test.

A study of two female patients diagnosed with glioblastoma and oligodendroglioma observed that a 12-week exercise programme significantly improved muscle strength, cardiovascular capacity and psychological indicators such as depression, anxiety and quality of life (39).

A study investigating the applicability and effectiveness of an individualised aerobic exercise programme for people undergoing brain tumour treatment found that performing moderate-intensity exercise for 20 minutes a day for six weeks led to significant improvements in parameters such as aerobic capacity, fatigue levels and functional independence. The exercise programme helped patients adapt to the treatment process (40).

Yoga and flexibility exercises have been used to reduce stress, improve flexibility and enhance general well-being in patients undergoing brain tumour treatment. Such exercises contribute to physical and psychological recovery (41).

Video-based exercise games are an innovative approach to developing balance and motor skills in children. Nintendo Wii Fit Plus games were used as an alternative to traditional exercise methods for children with brain tumours with significant improvements observed in balance tests (42).

Additionally, the American College of Sports Medicine's exercise prescription guidelines emphasise the effectiveness of exercise in alleviating anxiety, depressive symptoms and fatigue, while improving quality of life, physical function management, bone health and sleep. These findings suggest that all postoperative survivors should aim to participate in 150 minutes of moderate-intensity exercise as well as at least two resistance exercise sessions per week (43).

COGNITIVE REHABILITATION

Patients with brain tumours frequently exhibit cognitive deficits such as attention, memory and executive function disorders. Cognitive rehabilitation has been shown to improve these deficits (44).

A study was conducted to evaluate the effectiveness of a programme called Goal Management Training (GMT) in supporting executive functions in brain tumour patients. This programme, which incorporated mindfulness and strategy training, resulted in enhancements to cognitive and daily life functions (45).

Neuropsychological rehabilitation interventions should be incorporated into rehabilitation programmes to support patients with brain tumours and their caregivers (46). Cognitive rehabilitation programmes incorporating training in executive function, memory and attention skills and computer-based attention

training have been shown to improve neuropsychological performance, attention and memory and reduce psychological fatigue (47).

COMPLEMENTARY THERAPIES

Complementary therapies differ from alternative therapies. They are intended to be used alongside conventional medical treatments, complementing them. In contrast, alternative therapies are used instead of conventional medical treatments such as chemotherapy or radiotherapy. People with intracranial masses are interested in these approaches to improve their general well-being, build their immunity and manage their pain and other side effects.

The frequency with which these approaches are used by patients with tumours varies according to tumour type, age, gender and socioeconomic status (48). Recommended complementary therapies for individuals with intracranial masses include supplements such as L-carnitine and ginseng as well as acupuncture, yoga, massage and Reiki (20).

Acupuncture: This therapy involves placing thin, sterile needles at specific points on the body. It can alleviate symptoms such as pain, nausea, dry mouth, hot flushes, fatigue and shortness of breath by stimulating the release of natural painkillers such as endorphins.

Aromatherapy: This therapy uses herbal oils such as lavender, rosemary, eucalyptus and chamomile, which can be applied to the skin through massage, added to a hot bath, or diffused into the air using aromatherapy diffusers. Aromatherapy can provide support in dealing with anxiety, pain, depression, stress and fatigue.

Massage therapy and reflexology: These therapies are used to reduce muscle tension, relieve pain and promote relaxation. They can be useful in managing stress, anxiety and physical symptoms.

Talk therapies: Counselling, psychotherapy and cognitive behavioural therapy can help people cope with emotional difficulties such as stress, fear, anxiety and depression that can occur following a brain tumour diagnosis.

Breathing and relaxation exercises: These techniques can be learnt through support groups or at home using audio recordings and podcasts. They are used to reduce anxiety and stress, relieve muscle tension and improve digestion.

Visualisation and meditation: These techniques are used to calm and relax the mind and can help reduce stress and anxiety levels.

Hypnotherapy: It can be used to reduce the side effects of treatment such as nausea and vomiting and to relieve pain.

Arts and crafts therapy: This therapy uses activities such as painting, embroidery or sculpture to support emotional wellbeing by providing a way of expressing emotions.

Music therapy: This therapy involves listening to music or playing an instrument and can be carried out individually or in groups. It can promote emotional expression and relaxation.

In summary, complementary medicine methods such as acupuncture, cupping, music therapy, herbal medicine and reflexology can be used to alleviate tumour-related symptoms but further research is required to confirm their effectiveness. Additionally, orthoses, assistive devices and compensatory strategies can be useful in alleviating pain (49).

RECOMMENDATIONS FOR PHYSIOTHERAPY AND REHABILITATION IN THE POSTOPERATIVE ACUTE PERIOD

Individuals with intracranial masses require appropriate treatment during the acute postoperative period to enhance motor function, prevent complications arising from immobility such as pressure sores, muscle atrophy and contractures and to improve quality of life (20).

During this period, specific disorders and functional abilities are the primary issues to be considered. Patients with some voluntary motor control are encouraged to use the affected extremities in functional tasks. Those with persistent functional deficits are taught compensatory strategies.

Lower limb orthotic devices may be recommended for patients with persistent weakness such as drop foot or knee instability, if ankle and knee stabilization will help them to walk.

Cognitive and perceptual disorders can also cause motor dysfunction in individuals with intracranial masses. Language disorders affecting expression and comprehension, hemineglect and the inability to express needs, as well as the inability to understand motor commands and impairments in motor rehabilitation and cognitive deficits that prevent learning such as a lack of body awareness, make it difficult to implement active rehabilitation. Treatments emphasise re-education and the replacement of intact abilities as well as compensatory approaches.

The treatment of aphasia aims to improve comprehension, functional communication, and the use of strategies to compensate for persistent problems.

The treatment of hemineglect and other right-hemisphere language disorders focuses on raising awareness of deficits, restoring the pragmatics of non-verbal communication and teaching compensatory strategies such as the use of the affected side.

Discharge planning begins at the time of admission to an active rehabilitation programme and involves the interdisciplinary team, the patient and their family. Discharge occurs when treatment goals have been achieved or when there has been no progress for one to two weeks. This indicates that the treatment modality or rehabilitation setting needs to be reconsidered. Patients who are not suitable for active rehabilitation interventions may still benefit from home therapies or more passive interventions in another setting (6).

PALLIATIVE REHABILITATION IN INTRACRANIAL MASSES

According to the World Health Organisation, palliative care is an approach that aims to improve quality of life in cases of life-threatening disease. It includes practices that address the physical, psychological, social and spiritual needs of individuals.

Palliative care reduces unnecessary hospitalizations and the use of health services. It includes services provided by a multidisciplinary team, including physicians, nurses, physiotherapists, paramedics, pharmacists and volunteers, to support patients and their families (50).

The philosophy of palliative care is to adopt a person-centred approach, taking into account the individual wishes and preferences of patients (51).

The role of physiotherapists in palliative care is to:

- Pain management and relaxation

- Positioning (important for preventing pressure sores, helping digestion and preventing contractures).

- Endurance training and energy conservation techniques.

- Safety instructions for walking, climbing and descending stairs and transfers

- Therapeutic exercise

- Oedema management

- Equipment recommendations and modifications

- Home modifications (52).

FACTORS PREVENTING ACCESS TO REHABILITATION IN INDIVIDUALS WITH INTRACRANIAL MASSES

Although rehabilitation appears to be an easily accessible service for individuals with intracranial masses, implementation can be challenging due to insurance coverage issues, potential physical and cognitive barriers to participation and the absence of rehabilitation as part of multidisciplinary clinical care pathways and approaches.

Another problem is that the tumour and its treatment can cause physical, cognitive and emotional symptoms that reduce a patient's ability or motivation to participate in a rehabilitation programme. The minimum requirements for admission to an active inpatient or outpatient programme are active patient engagement, medical stability, one or more permanent disabilities, the ability to learn and the endurance to sit supported for at least one hour a day. Patients who do not meet these criteria have limited access to active rehabilitation programmes (6).

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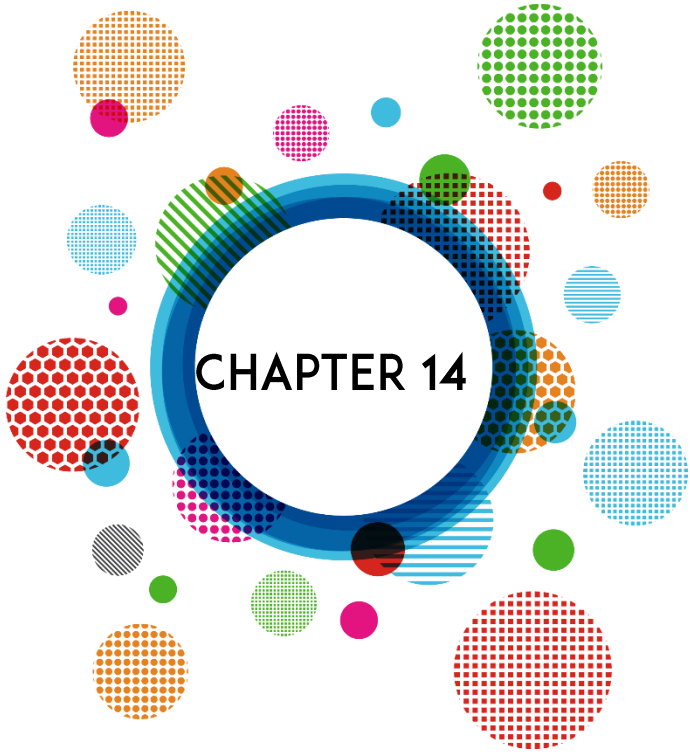

An Examination of the Effects of Children's Temperamental Traits and Parental Attitudes on Aggressive Behaviors

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INTRODUCTION

Adolescence represents an important transition period between the ages of 10 and 19; characterized by physical, sexual, cognitive, personality and psychosocial changes (WHO, 2023; Arı, 2008;). It is a stage where social connections and the search for independence intensify (Griffin, 2017).

This period also indicates increased vulnerability to emotional and behavioral disorders linked to impaired emotional regulation, including aggression, which is a common problem in mental health admissions (Ahmed et al., 2015; Saomah et al., 2020). Lynne-Landsman et al. (2011) observed an increase in aggressive behavior throughout adolescence, with 51% of adolescents reporting increased aggression by the end of secondary school.

Aggression, defined as antisocial behavior that aims to harm others, can occur in physical, verbal or relational forms (Krahé, 2013). Investigating the factors underlying aggression is very important for effective prevention and control (Li et al., 2012). This is because aggressive behaviors during adolescence increase the risks for future criminal activities, academic problems and interpersonal communication difficulties (Conger et al., 2003). Addressing these behaviors is essential for a healthy transition to adulthood (Mental, 2019). The etiology of aggression includes biological, psychological and social factors (Yalom, 2021).

Since parents are role models for children, their attitudes towards children are important and these attitudes are classified as democratic, authoritarian and indifferent (Kaya et al., 2012). Supportive and supervised parenting promotes better mental well-being and reduces the tendency to crime (Hair et al., 2008). Negative parent-adolescent relationships may lead to increased aggression (Chęć et al., 2016).

The term ‘temperament’, a set of inherited personality traits that emerge early in life, is defined as attitudes and behaviors associated with the foundation found in human structure, genetics and biology, and is used to describe the basic, intrinsic characteristics of a person that remain constant throughout life (Goldsmith et al. 1987; Goodwin & Jamison, 1990). Temperament affects both child and parent behaviors, emotions and cognition (Selçuk & Yılmaz, 2018). Studies show that early assessment of temperament can predict behavioral outcomes (Rothbart & Ahadi, 1994). Rothbart's (2007) research associates temperament with empathy, aggression and behavioral disorders

Starting in the 1960s, numerous studies have been undertaken to gain a deeper insight into the structure and significance of temperament. Particularly, developmental psychology experts have proposed various models. However, significant debates surrounding the exact definition and model of temperament, as well as the most appropriate methodology for its measurement, continue to persist (De Pauw & Mervielde, 2010). The Nine Types of Temperament Model (NTTM),

derived from the Enneagram System, provides insights into the differences between individuals (Yılmaz et al., 2014). The nine types are:

NTTM1: The pursuit of excellence

NTTM2: Sensation seeking

NTTM3: Quest for self-image

NTTM4: Search for meaning (emotion)

NTTM5: Search for meaning (knowledge)

NTTM6: The search for intellectual tranquility

NTTM7: Quest for discovery

NTTM8: Quest for power

NTTM9: Seeking physical comfort (Selçuk & Yılmaz, 2018; Yılmaz et al., 2014).

OBJECTIVE OF THE RESEARCH

The main objective of this study is to investigate whether parental attitudes and children's temperament traits influence their aggressive behaviors. In accordance with this overarching aim, the following question will be examined:

1. Does a meaningful statistical correlation exist between children's temperament traits and the aggressive behaviors they exhibit?

2. Do the temperament characteristics of children predict the aggression behaviors exhibited by children at a statistically significant level?

3.Is there a statistically significant relationship between parental attitudes towards children and aggression behaviors exhibited by children?

4.Do parental attitudes towards children predict the aggression behaviors exhibited by children at a statistically significant level?

5. Do the demographic characteristics of the child and parents (such as the child's sex, age, sibling count, birth position, parents' educational background, household income, family composition, marital status, and employment status) have a statistically significant impact on the aggressive behaviors demonstrated by children?

MATERIALS AND METHODS

Research Model

This study utilized a relational survey design, which is a quantitative research method. The relational survey approach seeks to determine if, and to what degree, variations exist between two or more variables (Karasar, 2023). The independent variables were parental attitudes, children's temperament characteristics, and demographic information, while the dependent variable was aggressive behaviors. The main aim of the study was to investigate how parental attitudes and children's temperament traits influence their aggressive behaviors

Participants

The study's sample includes students from public middle schools and their parents in the province of Karaman, Türkiye. The sample consisted of 211 students aged 11-14 years (133 girls %63.03, 78 boys %36.97) and their parents who agreed to participate. A convenience sampling approach was applied, and the sample size was determined using the G-power program with α=0.05, an effect size of 0.25, and a power level of 0.95.

Data Collection Tools

Demographic Information Form

This form, designed to gather personal details, was created to collect data on the socio-demographic attributes of both children and their parents. It contains questions intended to obtain information about the child's age, sex, grade, birth position, marital status, education, employment status, household income, and the number of children in the family.

Nine-Type Temperament Scale for Adolescents (NTTS-A)

The NTTS-A, created by Yılmaz et al. (2014), is used to evaluate the temperament types of adolescents. This scale comprises 82 items and utilizes a 3-point Likert scale with responses of 'Yes,' 'Sometimes,' and 'No.' Each question is specifically designed to assess the emotional and behavioral traits of individuals for each temperament type. The scale's internal consistency ranges from 0.88 to 0.92, and its validity has been supported by various studies

Children Aggression Scale-Parent Version (CAS-P)

Originally developed by Halperin et al. (2002) and adapted into Turkish by Ercan et al. (2016), this scale assesses children's aggressive behaviors. It consists of 28 items and four subscales, utilizing a five-point Likert scale from 'Never' to 'Most of the time.' The scale has an internal consistency of 0.93, and the reliability coefficients

for the subscales range from 0.62 to 0.90, confirming the tool's measurement validity.

Parenting Attitude Scale C Form (PAS C Form)

The PAS-C Form, created by Özyürek (2018), is used to assess children's attitudes as perceived by their parents. The scale comprises three sub-dimensions with a total of 35 items, employing a five-point Likert scale. The internal consistency of the scale, measured using Cronbach's alpha, was found to be 0.83 for Democratic Attitude, 0.83 for Oppressive and Authoritarian Attitude, 0.83 for Tolerant Attitude, and 0.75 for Extremely Tolerant Attitude. Additionally, the p-value of the item averages for the first and last 27% groups was found to be less than 0.01.

Procedure

Throughout the data collection process, participants were informed about the study's purpose and confidentiality. The data collection instruments were administered to adolescents from 5th, 6th, 7th, and 8th grades, along with their parents, in Karaman province, Türkiye, who voluntarily participated and provided their consent

Data Analysis

The data collected in the study were analyzed using SPSS 27.00 and RStudio software, transformed into tables, and included in the study. In assessing the normality of the data, the Kolmogorov-Smirnov test indicated that the NTTS-A data followed a normal distribution ($p>0.05$), while the ASC-PF and PAS-C data did not ($p<0.05$). For the first and third research questions, Spearman correlation analysis was conducted, whereas quantile regression was applied to the second and fourth questions. Additionally, the Mann-Whitney U test and Kruskal-Wallis H test were used to analyze the fifth question.

Quantile regression, which is a modelling technique applied in questions 2 and 4, is preferred if there is variance or outliers in the data set. This analysis method allows the effects of independent variables to be investigated in different percentiles of the dependent variable (Koenker, 2005).

RESULTS

In this section of the research, it was examined whether the parenting attitudes applied to children and the temperament characteristics of children affected their aggressive behaviors. The findings are presented according to the questions included in the research objectives.

The Spearman correlation analysis results for the first research question are provided in Table 1.

Table 1. Spearman Correlation Test Between Aggression Scores and Temperament Types

Dimension	Dimension	N	r	p
NTTM1	Total Aggression Score	211	-,165*	,017
	Verbal Aggression Score	211	-,156*	,023
NTTM8	Total Aggression Score	211	,248**	<,01
NTTM9	Total Aggression Score	211	-,252**	<,01

***p < 0.05**

****p < 0.01**

Based on the data in Table 1, it is seen that the level of aggression in children with dominant NTTM1 and NTTM9 temperament types decreases, while the level of aggression in children with dominant NTTM8 temperament type increases. No meaningful statistical variation was found between aggression levels and the other six temperament types Additionally, Table 1 shows a statistically significant negative relationship between verbal aggression and children with a dominant NTTM1 temperament type.

To address the second research question, regression analysis was conducted, and a heteroskedasticity test was performed using RStudio software due to the non-normal distribution of the data. The results of the test revealed a BP (Breusch-Pagan) statistic of 34.047, with 12 degrees of freedom (df) and a p-value of 0.0006632 (<0.05), indicating the presence of heteroskedasticity. Consequently, quantile regression analysis was carried out, and the results are shown in Table 2

Table 2. Quantile Regression Analysis Between Temperament Types and Aggression Scores

Quantile (Tau)	Independent Variable	Coefficient	Lower Bound (Lower BD)	Upper Bound (Upper BD)	Significance (Does Not Contain 0?)
0.25	(Intercept)	3.96622	-1.56406	9.23461	No
	NTTM1	-0.18250	-0.58683	0.01420	No
	NTTM8	0.19893	0.01214	0.34461	Yes*
	NTTM9	-0.33003	-0.54392	-0.07722	Yes*
0.50	(Intercept)	20.10488	11.77356	28.24283	Yes*
	NTTM6	0.27917	0.02239	0.52734	Yes*
	NTTM8	0.28468	0.11740	0.51441	Yes*
	NTTM9	-0.36202	-0.74879	-0.01616	Yes*
0.75	(Intercept)	49.11079	34.35790	57.39280	Yes*
	NTTM6	0.36147	0.03258	0.61040	Yes*
	NTTM8	0.76854	0.42739	1.05146	Yes*
	NTTM9	-0.68409	-1.02487	-0.20959	Yes*

*** Confidence interval does not include 0**

According to Table 2, the effects of certain temperament traits on different quantiles of aggression levels (lower 25%, median 50%, and upper 75%) are statistically significant. This indicates the varying impacts of the variables based on aggression levels, as shown below:

Lower Quantile (25%): At low aggression levels:

NTTM8 exerts a positive and statistically significant impact (coefficient: 0.19893), while NTTM9 has a statistically significant negative impact (coefficient: -0.33003)

Median Quantile (50%): At moderate aggression levels:

NTTM6 (coefficient: 0.27917) and NTTM8 (coefficient: 0.28468) exhibit significant positive effects, while NTTM9 shows a significant negative effect (coefficient: -0.36202).

Upper Quantile (75%): At high aggression levels:

NTTM6 (coefficient: 0.36147) and NTTM8 (coefficient: 0.76854) demonstrate significant positive effects, whereas NTTM9 has a notable negative effect (coefficient: -0.68409).

The findings from the Spearman correlation analysis performed to address the third research question are displayed in Table 3.

Table 3. Spearman Correlation Test Between Aggression Scores and Parenting Attitudes

Dimension	Dimension	N	r	p
Democratic Attitude	Total Aggression Score	211	-,151*	,029
	Unprovoked Physical Aggression Score	211	-,136*	,048
	Verbal Aggression Score	211	-,206*	,003
Authoritarian Attitude	Unprovoked Physical Aggression Score	211	-,170*	,013

***p < 0.05**

Based on the data in Table 3, a statistically significant negative correlation exists between democratic attitude and children's aggression levels ($p<0.05$).This means that as democratic attitude increases, children's aggression level decreases. The relationship between other attitudes and children's aggression levels was not significant.

Additionally, as indicated in Table 3, a statistically significant negative correlation is found between the unprovoked physical aggression sub-dimension scores and both democratic attitude and oppressive-authoritarian attitude ($p < 0.05$).

Table 3 reveals a statistically significant negative correlation between democratic attitude and the verbal aggression sub-dimension.

To address the fourth research question, quantile regression analysis was conducted based on the results of the heteroskedasticity test, as the data were not normally distributed, similar to the second research question. The results of this analysis are provided in Table 4.

Table 4. Quantile Regression Analysis Between Parental Attitudes and Aggression Scores

Quantile (Tau)	Independent Variable	Coefficient	Lower Bound (Lower BD)	Upper Bound (Upper BD)	Significance (Does Not Contain 0?)
0.75	(Intercept)	49.11079	34.35790	57.39280	Yes*
	Democratic attitude	-0.44695	-0.68579	-0.15233	Yes*
	Authoritarian attitude	-0.23614	-0.46701	-0.03278	Yes*

***Confidence interval does not include 0**

Table 4 shows that the effects of some parental attitudes are statistically significant only in the upper quantiles of aggression levels (lower 25%, median 50%, and upper 75%). The effects of these variables depending on the levels of aggression are shown below:

Upper Quantile (75%)

At high levels of aggression:

Democratic attitude is negatively significant (coefficient: -0.44695) and Oppressive-Authoritarian attitude is negatively significant (coefficient: -0.23614).

The outcomes of Mann-Whitney U and Kruskal-Wallis H tests to address the fifth research question are shown in Tables 5 and 6.

Table 5. Mann Whitney U-Test of Unprovoked Physical Aggression Scores According to the Gender of the Children

Gender	N	Mean Rank	Sum of Ranks	U	Z	p
Female	133	99,91	13287,50	4376,50	2,153	0.031*
Male	78	116,39	9078,50			

***p<,05**

To examine whether children's aggressive behaviors differ significantly based on demographic factors (such as child's gender, age, number of siblings, birth order, parents' education level, family income, family structure, marital status, and employment status), the Mann-Whitney U Test and Kruskal-Wallis H Test were applied.

The Mann-Whitney U Test analysis revealed no statistically significant difference in total aggression scores based on gender. However, as indicated in Table 6, a statistically significant difference was found in the unprovoked physical aggression subscale scores between groups based on children's gender ($p<0.05$). It was found that boys exhibit higher levels of unprovoked physical aggression compared to girls [$U=4376.50$, $p<0.05$].

Table 6. Kruskal-Wallis H Test for Unprovoked Physical Aggression Scores Based on Child's Birth Order

Birth Order	n	Mean Rank	df	Kruskal-Wallis H	
				X^2	P
First Child	96	114,24	2	7,627	0.022*
Middle Child	45	110,76			
Last Child	70	91,64			

p<,05

The Mann-Whitney U Test and Kruskal-Wallis H Test results revealed no statistically significant difference in total aggression scores based on variables such as the child's age, birth order, number of siblings, parents' education level, family income, family structure, parents' marital status, or parents' employment status. However, as shown in Table 6, the Kruskal-Wallis H Test identified a statistically significant difference in unprovoked physical aggression subscale scores according to children's birth order ($p<0.05$).

Following these significant findings, post-hoc comparisons were conducted to identify which groups contributed to the differences. For this objective, the Mann-Whitney U Test was utilized, and it was found that first-born children exhibited higher levels of unprovoked physical aggression compared to last-born children ($p < 0.05$).

DISCUSSION

Aggressive behaviors exhibited by children and adolescents are influenced by various factors, including biological, psychological, and environmental aspects. This study reveals that there is a link between parental attitudes, children's temperamental characteristics and aggressive behaviors.

In the study, no significant difference was found between genders in total aggression levels, but consistent with the existing literature, boys exhibited higher levels of unprovoked physical aggression (Gençoğlu et al., 2014; Köksal, 2016; Ayhan & Özkan, 2016). While total aggression scores were not significantly affected by factors such as age, birth order, family size and parental education, birth order affected unprovoked physical aggression, which first-born children showed higher levels than their last-born siblings (Çakır & Şen, 2012; Gençoğlu et al., 2014).

Temperament, which affects personality from the early stages of life, is linked to behavioral problems (Gagne, 2013). Some temperament characteristics may predict such problems (Caspi et al., 1995). The findings of the study showed that children with NTTM1 and NTTM9 temperaments had lower levels of aggression, while NTTM8 had higher levels of aggression. NTTM6 also showed positive associations with higher quantities of aggression. While NTTM1 children face challenges such as perfectionism and anger, they show responsibility and reliability while performing at their best (Bland, 2010). NTTM8 children often struggle with anger control and empathy (Yılmaz, 2010). NTTM9 children are typically calm and compliant (Acarkan & Zencer, 2021), while NTTM6 individuals, although cautious and sometimes indecisive, are successful in problem solving and reliability (Bland, 2010), but they tend to be open to reacting, irritable and very tense, especially in times of stress, with the influence of the NTTM3 wing (Selçuk & Yılmaz, 2018, pp.122.).

Parental attitudes significantly influence children's behavior. Authoritarian parenting emphasizing obedience often suppresses autonomy, whereas democratic parenting encourages open, supportive relationships and autonomy within limits (Baumrind, 1966; Vargas et al., 2021; Harahap & Sahputra, 2023). In this study, a negative relationship was found between democratic attitudes and authoritarian attitudes and children's aggression levels; democratic attitudes reduce aggression more effectively than authoritarian attitudes, especially at higher levels of aggression. While these findings are in line with studies emphasizing the stabilizing role of democratic attitudes, they are not in line with the results of authoritarian attitudes (Yıldız & Erci, 2011; Wei, 2023; Kulakci-Altintas & Ayaz-Alkaya, 2018), but may be considered to be related to authoritarian attitudes, which indicate increased irritability and internalizing problems such as depression and anxiety (Morris et al., 2002).

CONCLUSIONS AND RECOMMENDATIONS

In the current study, the effects of temperament characteristics of children and parental attitudes on aggressive behaviors were examined and significant results were obtained.

While children with the dominant NTTM8 (Power Seeking Temperament) exhibited higher levels of aggression, the aggression levels of children with dominant NTTM1 (Perfection Seeking Temperament) and NTTM9 (Comfort Seeking Temperament) decreased and the critical role of temperament in aggression was underlined.

Democratic parental attitudes significantly reduced children's aggression more effectively than authoritarian attitudes and emphasized the importance of democratic attitudes.

Demographic factors also influenced aggression, with boys exhibiting higher levels than girls and first-borns exhibiting more unprovoked aggression than last-borns.

Drawing from the results of the study, the following suggestions can be proposed:

Family counselling and educational programs can be developed to promote democratic parental attitudes by emphasizing positive parent-child relationships and effective discipline.

School-based programs focusing on anger management, empathy and problem solving can be developed to improve adolescents' emotional and social skills.

Individualized intervention plans can be developed for children with NTTM8 temperament that address specific temperament characteristics such as anger management.

Efforts can be made to increase awareness among parents and educators regarding the long-term impact of aggressive behaviors and campaigns can be organized against the normalization of domestic violence and media aggression.

Larger longitudinal studies can be conducted to investigate the relationship between temperament types, parental attitudes and aggression and the generalizability of the findings can be increased.

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