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Exercise and Mitochondrial Function in Neurodegenerative and Demyelinating Diseases

Nörodejeneratif ve Demyelinizan Hastalıklarda Egzersiz ve Mitokondriyal Fonksiyon

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Abstract

Neurodegenerative and demyelinating diseases have a major impact on patient longevity and quality of life, creating a serious risk to life, health, and well-being. These diseases have been associated with poor and malfunctioning mitochondria in the central nervous system. Mitochondria are vital for several biological processes, including the production of energy and reactive oxygen species, the regulation of calcium levels within cells, and the control of programmed cell death. Alterations in mitochondrial activity have a significant impact on the most prevalent neurodegenerative and demyelinating disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS). Exercise has been shown to improve muscle function and contribute to the muscle-brain interaction via various signaling pathways and molecular mechanisms (myokines, extracellular vesicles, and bioactive molecules etc.). The stimulation and subsequent training of skeletal muscle is a crucial aspect of exercise, with proven benefits for mitochondrial function. It is now known that exercise is a non-pharmacological method of preventing and reversing neurodegeneration and brain deterioration. Regular exercise enhances the survival and neuroplasticity of neurons and improves the body's reactions to stress in terms of mitochondria. This review presents an overview of current knowledge on the role of normal mitochondrial function, including mitochondrial biogenesis, dynamics, and mitophagy, as well as exercise and mitochondrial function, in neurodegenerative and demyelinating disorders. In the following sections, we also discuss how exercise affects mitochondrial processes in disorders such as AD, PD, MS, and ALS.

Keywords: Exercise, mitochondria, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis

Öz

Nörodejeneratif ve demyelinizan hastalıklar, hasta ömrü ve yaşam kalitesi üzerinde büyük bir etki yaratarak yaşam, sağlık ve refah için ciddi bir risk oluşturmaktadır. Bu hastalıkların, merkezi sinir sistemindeki hasarlı ve normal fonksiyonu bozulmuş mitokondrilerle çok yakından ilişkili olduğu gösterilmektedir. Mitokondri, enerji ve reaktif oksijen türlerinin üretimi, hücrelerdeki kalsiyum seviyelerinin düzenlenmesi ve programlanmış hücre ölümünün kontrolü gibi çeşitli biyolojik süreçler için hayati öneme sahiptir. Bununla birlikte, mitokondriyal aktivitedeki değişiklikler, Alzheimer hastalığı (AD), Parkinson hastalığı (PD), multipl skleroz (MS) ve amyotrofik lateral skleroz (ALS) gibi yaygın nörodejeneratif ve demyelinizan hastalıklar için kritiktir. Egzersizin kas fonksiyonunu iyileştirdiği, çeşitli sinyal yolakları ve moleküler mekanizmalar (miyokinler, hücre dışı veziküller ve biyoaktif moleküller vb.) yoluyla kas-beyin etkileşimine katkıda bulunduğu gösterilmiştir. İskelet kasının uyarılması ve antrene edilmesi, mitokondriyal fonksiyon için kanıtlanmış faydaları olan egzersizin çok önemli bir yönüdür. Egzersizin nörodejenerasyonu ve beyin hasarını önlemek için farmakolojik olmayan bir yöntem olduğu artık bilinmektedir. Düzenli egzersiz, nöronların hayatta kalmasını, nöroplastisitesini artırır ve vücudun mitokondri açısından strese verdiği tepkileri iyileştirir. Bu derleme, mitokondriyal biyogenez, dinamikler ve mitofaji dahil olmak üzere normal mitokondriyal fonksiyonun yanı sıra egzersiz ve mitokondriyal fonksiyonun nörodejeneratif ve demyelinizan bozukluklardaki rolü hakkındaki mevcut bilgilere genel bir bakış sunmaktadır. İlerleyen bölümlerde, egzersizin AD, PD, MS ve ALS gibi bozukluklarda mitokondriyal süreçleri nasıl etkilediği de tartışılmıştır.

Anahtar Kelimeler: Egzersiz, mitokondri, Alzheimer hastalığı, Parkinson hastalığı, multipl skleroz, amyotrofik lateral skleroz

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Introduction

The prevalence of neurodegenerative and demyelinating diseases is on the rise in parallel with the extension of human life expectancy. These conditions have significant implications for patient survival and quality of life, presenting a substantial hazard to life, health, and well-being (1). The functioning of the brain is dependent on adenosine triphosphate (ATP) levels, which is produced in large quantities by mitochondria through oxidative phosphorylation (OXPHOS). Neurons have a high metabolic demand and limited capacity for regeneration, making them particularly susceptible to the deleterious effects of mitochondrial dysfunction (2).

Mitochondria are indispensable for numerous biological functions, including energy and reactive oxygen species (ROS) production, calcium homeostasis, and cell death (3). Several vital biological processes, including the transportation of proteins, the formation of neuronal cell membrane potentials, and the transmission of signals, are unable to take place in the absence of energy provided by mitochondria (4).

Exercise has been postulated as a non-pharmacological intervention capable of modifying both brain structure and function (5). Regular exercise has significant beneficial effects on mitochondrial structure formation, with high-intensity exercise resulting in greater improvements in OXPHOS efficiency (6).

This review will center on elucidating the functions of mitochondria, as well as examining the impact of exercise-induced improvements in mitochondrial health on neurodegenerative and demyelinating diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).

Mitochondria and Normal Mitochondrial Function

Mitochondria, which developed through bacterial endosymbiosis, share striking similarities with archeabacterium (7). Although there are different views, an α-proteobacterium was engulfed by a predecessor of the current eukaryotic cell, resulting in the formation of mitochondria (8). Mitochondria are widely acknowledged as primary energy providers for cellular functions (9), with ATP production specifically tied to the efficiency of OXPHOS (10). Vital biological processes, such as protein transport, neuronal cell membrane potential generation, and signal transmission, rely on the energy supplied by mitochondria (4).

Mitochondrial Biogenesis

Healthy cells typically undergo mitochondrial biogenesis, a unique process for maintaining number, function, and energy production (11) (Figure 1). This process requires the synchronized transcription and translation of nuclear and mitochondrial genes located in both the nucleus and mitochondria since more than 90% of mitochondrial proteins are encoded by nuclear genes (12). The processes that comprise mitochondrial biogenesis include the replication of mitochondrial DNA (mtDNA), the synthesis of nuclear-encoded mitochondrial proteins, and the production of the inner and outer mitochondrial membranes (OMMs) and mitochondrial-encoded proteins (13).

Two main routes that control mitochondrial biogenesis are the sirtuin 1 (SIRT1)-peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and the adenosine monophosphate (AMP)-activated kinase (AMPK)-PGC-1α axis (14). Increased cellular energy demand activates the evolutionary cellular sensor known as AMPK, and mitochondrial bioenergetics and AMPK are closely related (15). PGC-1α can be immediately phosphorylated and activated by AMPK. The increase in PGC-1α expression and mitochondrial biogenesis may be due to AMPK activation (16). Additionally, PGC-1α is activated by SIRT1 (17). In an epilepsy model, SIRT1 activation improved hippocampal activity in rats by enhancing the PGC-1α/mitochondrial antioxidant signaling pathway (18).

Mitochondrial Dynamics

A mechanism known as mitochondrial dynamics regulates the size and structure of mitochondria through a repeated fusion and fission cycles (19) (Figure 1). The optic atrophy 1 protein, crucial for maintaining mitochondrial cristae structure, controls fusion on the inner mitochondrial membrane, while mitofusin-1 (MFN-1) and MFN-2 manage fusion on the OMM (20). The main mediator of mitochondrial fission is dynamin-related protein 1 (DRP1). Mitochondrial fission normally occurs in the cytoplasm. Under stress conditions, the four main adaptor proteins that attach cytosolic DRP1 monomers to the OMM are: Mitochondrial fission factor, mitochondrial fission 1 protein and mitochondrial dynamics proteins, which bind DRP1 to the OMM (21). To alleviate cellular dysfunction, prevent tissue deterioration and restore function, strategies aimed at balancing mitochondrial dynamics hold promise.

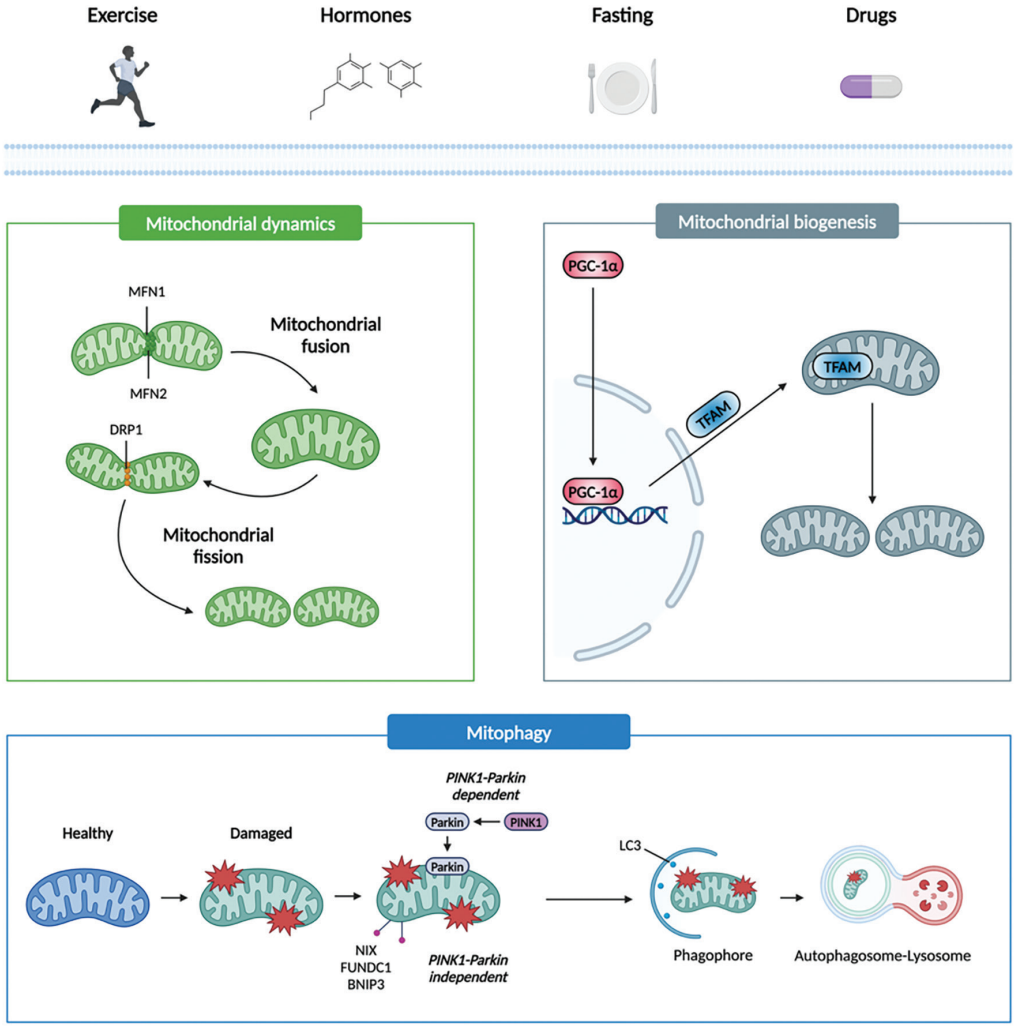

Figure 1: Components of mitochondrial adaptation to exercise, hormones, fasting, and drugs. Figure was created with BioRender.com

MFN1: Mitofusin-1, MFN2: Mitofusin-2, DRP1: Dynamin-related protein 1, PGC-1α: Proliferator-activated receptor gamma coactivator 1-alpha, TFAM: Transcription factor A, PINK1: Phosphatase and tensin homolog deleted on chromosome 10-induced putative protein kinase 1, NIX: NIP3-like protein X, FUNDC1: FUN14 domain containing 1, BNIP3: BCL2/adenovirus E1B 19 kDa protein-interacting protein 3, LC3: Microtubule-associated proteins 1A/1B light chain 3B

Mitophagy

The equilibrium between mitochondrial production and degradation determines mitochondrial mass, with mitochondrial biogenesis resulting in increased mitochondrial numbers, while a healthy mitochondrial population depends on the removal of defective mitochondria by mitophagy (22,23) (Figure 1). After the specific encapsulation of damaged mitochondria by the autophagosome, these mitochondria are transported to the lysosome where they fuse to form mature mitochondrial autolysosomes, which are then degraded by the lysosomes (24). Proteins located in the inner or outer membrane of mitochondria are known as mitophagy receptors, and contain microtubule-associated proteins 1A/1B light chain 3B (LC3)-interaction region (LIR) domain (25). Mitophagy receptor proteins selectively remove damaged mitochondria by interacting with the necessary autophagy protein LC3, mitophagy receptor proteins selectively destroy damaged mitochondria in response to various mitochondrial stresses, including reduction of mitochondrial membrane potential, oxidative stress, and other conditions, by interacting with the essential autophagy protein LC3 (26,27).

Damage or defect in the mitochondria results in the attachment of specific chemical markers, via the LC3 protein, to facilitate their identification and subsequent removal through a process known as mitophagy (28). Phosphatase and tensin homolog deleted on chromosome 10-induced kinase 1 (PINK1) accumulates on the OMM in the presence of cellular stress or mitochondrial depolarization, which attracts the E3 ubiquitin ligase Parkin (29). The OMM proteins mitofusins and other related proteins are ubiquitinated by the Parkin protein, which then forms polyubiquitin chains that serve as mitophagy signals (30).

The ubiquitin chains are bound by autophagy receptors such as optineurin and sequestosome-1, which interact with LC3 due to their LIR (31). This dual binding enables the mitochondria to be enclosed within an autophagosome for subsequent lysosomal destruction, thus maintaining cellular homeostasis. To fully realize the potential benefits of mitophagy without causing harm, there must be a balance in its activation.

The Effects of Exercise and Mitochondrial Dysfunction in Neurodegenerative and Demyelinating Diseases

The production of ATP and the quality control of mitochondria are of great importance in the context of neurodegenerative and demyelinating diseases, as these conditions are frequently characterized by mitochondrial dysfunction (32). Impaired OXPHOS results in a reduction of ATP levels, which in turn leads to energy deficits in neurons that are highly dependent on a steady energy supply (33). Concurrently, mitochondrial quality control mechanisms, including mitophagy, fission, and fusion, are disrupted, thereby exacerbating the accumulation of damaged mitochondria (34). For example, in PD, mutations in PINK1 and Parkin impair mitophagy, while in AD, altered mitochondrial dynamics contribute to the buildup of dysfunctional organelles (35,36). An understanding of these processes across various neurodegenerative and demyelinating diseases offers insight into common pathological mechanisms and potential therapeutic targets.

A growing body of research indicates that regular exercise can protect against chronic illnesses, delay the aging process, and improve overall health (37). Exercise induces perturbations in energy homeostasis in skeletal muscle, activating cellular signaling networks that facilitate the adaptation of skeletal muscle to the increased energy and oxygen demands associated with contraction-induced activity (38). High exercise capacity and mitochondrial function are clearly correlated, with mitochondria serving as the primary source of ATP and essential regulators of exercise capacity (39). Additionally, exercise enhances mitochondrial integrity and function by accelerating mitochondrial turnover, promoting efficient mechanisms for managing organelle turnover such as mitophagy and lysosome biogenesis (40). For example, exercise enhances mitochondrial functioning through its various physiological effects. Research indicates that exercise impacts hippocampal mitochondrial function, neuroplasticity, apoptosis, and increases levels of brain-derived neurotrophic factor (BDNF) (41).

Effects of Exercise and Mitochondrial Dysfunction in Parkinson's Disease

PD is defined by the gradual degradation of dopaminergic neurons, which finally results in a dopamine insufficient in the striatum (42). The pathophysiology of PD is closely linked to mitochondrial dysfunction and oxidative stress (43). A decrease in regulators of mitochondrial biogenesis has been demonstrated to result in a suppression of mitochondrial biogenesis in PD (44). Tissue samples from idiopathic PD patients who have post mortem have demonstrated higher mtDNA abnormalities, indicating mitochondrial malfunction in the disease (45). Several factors contribute to PD-associated mitochondrial dysfunction, including impaired mitochondrial biogenesis, elevated generation of ROS, impaired mitophagy, disrupted protein trafficking, and malfunctioning electron transport chain (ETC) (46).

After physical exercise, levels of BDNF, superoxide dismutase (SOD), and catalase increased in PD rats, while oxidative stress indicators for proteins and lipids decreased. These findings indicate that exercise improves oxidative stress markers and modulates the state of the neurochemicals (47) (Figure 2). Exercise training significantly reduced the loss of dopaminergic neurons in PD animals and improved neuronal and behavioral functions, accompanied by increased mitochondrial activity and neurotrophic factor levels in brain regions (37). In rats with PD, exercise training reduced oxidative stress, restore mitochondrial function, and enhanced dopaminergic neuron survival. This process may involve promoting mitochondrial turnover, including fission, fusion, and clearance, along with increasing mitochondria numbers (48). It has been demonstrated that treadmill exercise has shown promise in reducing α-synuclein accumulation in neurons and promoting the translation of biogenesis regulators and nuclear-encoded mitochondrial proteins. This may lead to an increase in mitochondrial biogenesis and the import of nuclear-encoded mitochondrial protein (49). Endurance exercise may be an effective method of enhancing cerebral mitochondrial biogenesis, thereby mitigating neural energy deficiencies in PD. In particular, treadmill training was observed to elevate or restore the levels of biogenesis regulators and import machinery (50).

Effects of Exercise and Mitochondrial Dysfunction in Alzheimer's Disease

AD is a neurodegenerative disease that affects millions of individuals worldwide and causes the brain to gradually and irreversibly deteriorate. ATP generation, the main energy source for cells, is impaired by mitochondrial dysfunction in AD. Amyloid beta-induced oxidative damage is connected to mitochondrial dysfunction in the early stages of AD (51). It is well established that amyloid beta can migrate to mitochondrial membranes, interfere with the ETC, produce more ROS, damage mitochondria, and impair normal neuron function (52). Increasing evidence suggests that defects in mitochondrial ETC

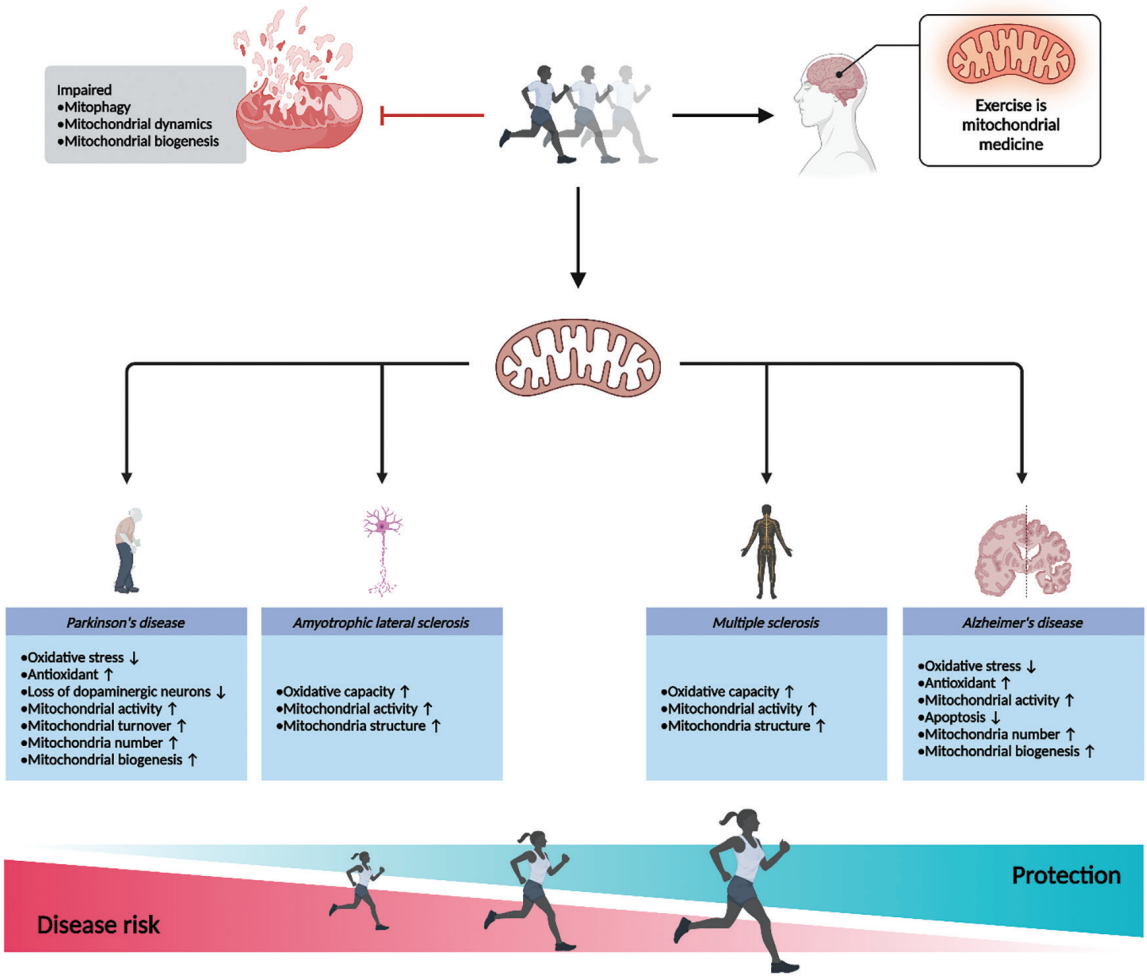

Figure 2: Relationship between exercise and mitochondrial dysfunction in neurodegenerative and demyelinating diseases. Figure was created with BioRender.com

enzymes and reduced efficiency of complex I and complex IV are associated with AD (53).

Exercise has been demonstrated to benefit several prominent symptoms of AD by regulating brain pathways associated with oxidative stress (54) (Figure 2). In addition, it has been shown that regular exercise significantly increases the metabolic rate and thus reduces the ROS level (55). While acute exercise may not have a significant effect on brain mitochondria, sustained exercise may decrease oxidative DNA damage and lipid peroxidation (56). Additionally, there has been evidence of elevation of mitochondrial antioxidant (SOD and catalase) activity in AD animal models treated to prolonged exercise (57). Six-day-a-week swimming exercise preserved the margins and cristae of the mitochondria, increased brain ATP generation, and enhanced synaptic density (58). The evidence suggests that exercise can serve as a therapeutic strategy to alleviate the deleterious effects of AD. These benefits are attributed to exercise's interactions with mitochondrial functions, including redox balance, enhancement of bioenergetics, apoptosis blocking, and inducement of mitochondrial biogenesis in AD.

Effects of Exercise and Mitochondrial Dysfunction in Multiple Sclerosis

MS is a long-term autoimmune disorder highlighted by demyelination, inflammation, neuronal death, and scarring (59). Mitochondrial dysfunction is increasingly recognized as a significant component of MS pathology, impacting the clinical course of the disease. Damage to mitochondria results in energy deprivation, leading to dysfunction in neuronal signal transmission (60). Oxidative damage, marked by the formation of oxidized lipids, proteins, and DNA, is observed in the process of cellular degeneration within the dynamic and progressively increasing lesions typical of MS (61). Inflammation in MS contributes to energy depletion and mitochondrial dysfunction, further exacerbating neuronal deterioration (62). MS also affects mitochondrial dynamics in neurons, including fission

and fusion processes. Defects in mitochondria and subsequent energy failure can disrupt other cellular processes, contributing to increased demyelination and inflammation in affected neurons and tissues (63).

It is well documented that people with MS benefit from regular exercise, which improves motor function, reduces fatigue, and enhances cardiorespiratory fitness (64) (Figure 2). Mitochondrial enzymes in individuals with MS have shown reduced succinate dehydrogenase activity across all types of muscle fibers, suggesting a greater reliance on anaerobic rather than aerobic oxidative ATP production compared to healthy individuals (65). Changes in muscle fiber dimensions and composition associated with MS are accompanied by alterations in muscle mitochondrial content (66). A cross-sectional study found a positive correlation between walking performance and physical activity levels in people with MS. The study results indicated that walking performance correlates positively with brain volume, fatigue levels, cognitive processing speed, and tract integrity (67).

Effects of Exercise and Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis

ALS, characterized by motor neuron atrophy in the nervous system, is the most common form of motor neuronopathy in adults (68). Substantial evidence links ALS pathology to progressive changes in mitochondrial structure, bioenergetics, and calcium homeostasis (69). Motor neurons derived from ALS patients exhibit altered structural features and mitochondrial clustering, characterized by enlarged and vacuolated organelles (70). ALS patients also demonstrate reduced activity in all complexes of the ETC, including complexes I, II, III, and IV (71). Excessive production of ROS in ALS contributes to oxidative damage across cellular components, particularly affecting mitochondria, which are highly susceptible to such damage (72). Furthermore, increased ROS generation promotes muscle atrophy in ALS (73).

It has been demonstrated that regular exercise can have beneficial effects on muscular strength and oxidative capacity in healthy individuals. Therefore, exercise can be regarded as a potentially viable therapeutic option for patients suffering from ALS (74) (Figure 2). Clinical trials suggest that exercise can enhance lung function and functional capacity in ALS patients, primarily demonstrated over the long term, with limited benefits observed in the short or medium term (75). It has previously been debatable whether exercise increases the risk of ALS (76). In ALS, it is the type IIB muscle fibers that are most vulnerable to the disease's progression. These fibers are responsible for anaerobic activity, and there is evidence that ALS is particularly associated with strenuous exercise (76-78). It has been demonstrated that swimming exercise results in modifications to the structure and function of mitochondria, which can be attributed to alterations in the concentration of mitochondrial cholesterol (79). Furthermore, numerous studies have indicated that individuals with ALS exhibit abnormal physiological responses to exercise (80). Prolonged periods of high-intensity exercise have been shown to exacerbate several adverse effects on the body, including motor neuron denervation, irreversible strength loss, and muscle degeneration (81). It has been suggested that moderate exercise programs may be beneficial for people with ALS, potentially impacting free radical balance and muscle fiber oxidation (82,83).

It is possible that excessive exercise may overload the antioxidant systems of ALS patients, which are already compromised, and increase the generation of ROS (84). This could result in further harm to nearby tissues and neurons. Moreover, the capacity to recuperate muscles following strenuous exercise is compromised by the progressive loss of motor neurons and ensuing muscular atrophy associated with ALS (85). The progression of the disease may be accelerated by overexertion, which can lead to increased fatigue and accelerate the degeneration of motor neurons (85). The findings of research conducted on animals and observations made by patients indicate that moderate, tailored exercise may improve quality of life and potentially slow the progression of symptoms (83). However, excessive or uncontrolled exercise has been shown to have adverse effects (81). It is therefore imperative that exercise regimens are tailored to the individual and designed to avoid overexertion to effectively manage ALS.

Conclusion

Exercise has been recognized as a non-pharmacological intervention with neuroprotective effects in neurodegenerative and demyelinating disorders. Its mechanism involves modulating multiple brain pathways, with mitochondria being a significant target organelle affected by physical activity. Exercise plays a crucial role in preventing and treating neurodegenerative and demyelinating diseases by interacting with mitochondrial mechanisms, including redox control, bioenergetics, reduced apoptosis, stimulation of mitochondrial biogenesis, and modulation of mitochondrial dynamics and mitophagy.

It is of the utmost importance that future studies concentrate on elucidating the complex relationships between human activity and mitochondrial function, particularly in the context of neurodegenerative and demyelinating disorders. An investigation into the influence of exercise on mitochondrial biogenesis, dynamics and quality control may facilitate the development of targeted treatment approaches. One promising avenue of research is the utilization of wearable technology, such as sensors, to monitor mitochondrial biomarkers and physiological responses in real-time. These techniques may enable the precise measurement of mitochondrial responses to

various exercise regimens, aiding in the optimization of duration and intensity for maximal benefit. These advancements may pave the way for the development of personalized therapies that enhance outcomes while reducing risks for susceptible groups.

Footnotes

Authorship Contributions

Concept: G.B.K., İ.T., İ.M.D., Design: G.B.K., İ.T., İ.M.D., Literature Search: G.B.K., İ.T., İ.M.D., Writing: G.B.K., İ.T., İ.M.D.

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Romatolojik Hastalıklarda COVID-19: Tek Merkez Deneyimi

COVID-19 in Rheumatic Diseases: A Single Center Experience

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Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu, Mart 2020'de pandemi olarak ilan edildi ve tüm dünyayı etkisi altına aldı. Pandeminin başından itibaren romatolojik hastalığı olanlar ve immünosüpresif ilaç kullananlarda COVID-19'un morbidite ve mortaliteye etkisi merak edildi.

Gereç ve Yöntem: Bu çalışmaya, Ağrı ilinde Kasım 2018-Haziran 2021 tarihleri arasında romatoloji polikliniğine başvurup romatolojik hastalık tanısı ile izlenen hastalar dahil edildi. Demografik, romatolojik hastalık ilişkili ve COVID-19 verilerine retrospektif olarak ulaşıldı.

Bulgular: Çalışmaya dahil edilen 1.170 hastanın %58,6'sı (686) kadın, %41,4'ü (484) erkekti, ortalama yaş 45,6±15,7 ve hastaların %18,9'unda (221) COVID-19 tespit edildi. COVID-19 pozitif hastaların hospitalizasyon oranı %13, yoğun bakım yatış oranı %5, ölüm %3,2, bilgisayarlı tomografi ile saptanmış akciğer tutulum oranı %19 izlendi. COVID-19 pozitifliği cinsiyet (p=0,04), sülfasalazin (SLZ) kullanımı (p=0,01), hipertansiyon (HT) (p=0,02) ve yaş (p=0,008) ile ilişki saptandı. COVID pozitifliği risk faktörlerinin belirlenmesi için yapılan regresyon analizinde yalnızca SLZ kullanımı 2,1 kat COVID risk artışı ile ilişkili bulundu. COVID-19 pozitif hasta popülasyonunda ölüm ile rituksimab kullanımı (p<0,001), HT (p=0,001) ve yaş (p=0,001) ile ilişki saptandı. COVID-19 pozitif hastalarda ölüm risk faktörlerinin belirlenmesi için yapılan regresyon analizinde yalnızca yaş ölüm riski ile ilişkili bulundu.

Sonuç: Tek merkezde takipli romatoloji hastalarının COVID-19 deneyiminin paylaşıldığı bu çalışma ile romatoloji hastalarında COVID-19 sıklığı Türkiye geneli ile benzer oranda, COVID-19'a bağlı ölüm ise yaş ile ilişkili bulundu.

Anahtar Kelimeler: COVID-19, romatoloji, morbidite, mortalite

Abstract

Objectives: Coronavirus disease-2019 (COVID-19) infection was declared a pandemic in March 2020 and has affected the entire world. Since the beginning of the pandemic, there has been concern about whether patients with rheumatic diseases are at an increased risk of COVID-19-related morbidity or mortality.

Materials and Methods: In this study, patients who applied to the rheumatology outpatient clinic in the Ağrı province between November 2018 and June 2021 and were followed up with a diagnosis of rheumatologic disease were included. Rheumatological diseases, demographics, and COVID-19 data were collected retrospectively.

Results: Of the 1,170 patients included in the study, 58.6% (686) were female and 41.4% (484) were male, the mean age was 45.6±15.7 years and 18.9% (221) of the patients were COVID-19 positive. COVID-19 positive patients had a hospitalization rate of 13%, an intensive care unit stays rate of 5%, a mortality rate of 3.2%, and a computed tomography-detected lung involvement rate of 19%. COVID-19 positivity was associated with gender (p=0.04), sulphasalazine (SLZ) use (p=0.01), hypertension (HT) (p=0.02) and age (p=0.008). In the regression analysis performed to determine the risk factors for COVID positivity, only SLZ use was associated with a 2.1-fold increase in COVID risk. In the COVID-19 positive patient population, death was associated with rituximab use (p<0.001), HT (p=0.001) and age (p=0.001). In the regression analysis performed to determine the risk factors for death in COVID-19 positive patients, only age was associated with the risk of death.

Conclusion: In this study, the COVID-19 experience of rheumatology patients was followed up in a single center; the frequency of COVID-19 in rheumatology patients was found to be similar to Türkiye in general; and death from COVID-19 was found to be age-related.

Keywords: COVID-19, rheumatology, morbidity, mortality

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Giriş

Aralık 2019'da Çin'de başlayıp kısa sürede tüm dünyaya yayılan yeni koronavirüs etkeninin yol açtığı koronavirüs hastalığı-2019 (COVID-19) 11 Mart 2020'de Dünya Sağlık Örgütü tarafından pandemi olarak bildirildi. Ülkemizdeki ilk COVID-19 olgusu ise 10 Mart 2020'de tespit edildi. COVID-19 hastalığı asemptomatik olabileceği gibi; ateş, üst solunum yolu enfeksiyonu bulguları, miyalji, artralji gibi hafif-orta semptomlar görülebilmekte ve yaklaşık %5 olguda ciddi hastalık bulguları gelişebilmektedir (1). Ciddi hastalık seyrinde sitokin fırtınası, akut respiratuvar distres sendromu ve çoklu organ yetmezlik tablosu nedeni ile yüksek morbidite ve mortalite oranları bildirilmektedir. Ciddi hastalık, özellikle yaşlı ve obezite, hipertansiyon (HT), diabetes mellitus (DM), kronik obstrüktif akciğer hastalığı, kardiyovasküler hastalık, kronik böbrek yetmezliği, kanser gibi komorbiditesi olan hastalarda daha sık görülmektedir (2).

Pandeminin başından itibaren, immünosüpresif tedavi altındaki ve altta yatan immün düzensizlikleri olan romatoloji hastalarında COVID-19 riski veya hastalık şiddetinin genel nüfusa göre artıp artmadığı merak konusu olmuştur. Bu konuda çelişkili çalışmalar olup, pandeminin başından beri elde edilen veriler biyolojik veya sentetik hastalık modifiye edici ajanlarla (DMARD) tedavi edilen enflamatuvar romatizmal hastalığı olan bireylerde COVID-19 şiddetinin arttığı doğrulanamamıştır. Pandeminin erken dönemlerinde üç farklı çalışmada romatoid artrit (RA), spondiloartrit ve psöriatik artrit (PsA) hastalarında COVID-19 sıklığı genel popülasyon ile benzer bildirilmiş (3-5). Bağ doku hastalıklarından skleroderma (Scl) hastalarında ise COVID-19 sıklığı üç farklı İtalyan çalışmasında genel popülasyondan yüksek bulunmuştur (6). Ailevi akdeniz ateşi (FMF) hastalarının değerlendirildiği çalışmalarda COVID-19 ile enfekte olma, hastaneye yatış ve mortalite oranlarının normal popülasyonla benzer olduğu bildirilmiştir (7,8). Komorbid hastalığı olmak, proteinüri varlığı, interlökin-1 inhibitör kullanımı hastanede yatan hastalarda daha yüksek olma eğiliminde bulunmuştur (9,10). Antinötrofil sitoplazmik antikorlar (ANCA) ilişkili vaskülit tanılı 100 hastanın genel popülasyonla karşılaştırıldığı bir çalışmada, COVID-19 insidansı ANCA ilişkili vaskülitte genel popülasyona göre daha düşük bildirilmiştir (sırasıyla %2 ve %6,3) (11). Diğer taraftan COVID-19 ilişkili hastaneye yatış ve mortalite oranlarının romatolojik hastalıklar ve genel popülasyonla karşılaştırıldığı bir Danimarka çalışmasında romatolojik hastalığı olanlardan özellikle RA ve vaskülit hastalarında hastaneye yatış oranları yüksek saptanmıştır (12).

Avrupa ve Amerika Romatoloji Dernekleri romatolojik hastalığı olan bireylerde olmayanlara göre COVID-19 riskinin artmadığını ve virüsle karşılaşanlarda prognozun daha kötü olmadığını bildirmiştir (13,14). Romatolojik hastalıklarda COVID-19 riskinin arttığını bildiren çalışmalar küçük bir ek risk artışının olduğunu, kötü prognozun ise komorbiditelerin varlığı, steroid veya rituksimab (RTX) kullanımı ve yüksek hastalık aktivitesi ile ilişkili olduğunu savunmaktadır (15).

Bu çalışmada, tek bir merkezde takip edilen enflamatuvar romatolojik hastalığı olan bireylerde COVID-19 sıklığı ve prognozunun retrospektif olarak değerlendirilmesi amaçlanmıştır. Ayrıca COVID-19 pozitifliği ve mortalite ile ilişkili faktörlerin belirlenmesi ikincil sonlanım noktalarını oluşturmaktadır.

Gereç ve Yöntem

Kasım 2018-Haziran 2021 tarihleri arasında Ağrı Eğitim ve Araştırma Hastanesi, Romatoloji Polikliniği'ne başvurup enflamatuvar romatolojik hastalık tanısı ile izleme alınan ve tedavi başlanan hastalar geriye dönük olarak değerlendirildi. Romatoloji polikliniğine başvurup tanısı netleşmeyen veya osteoartrit, fibromiyalji gibi enflamatuvar hastalık tanısı almayan hastalar dahil edilmedi. Enflamatuvar romatolojik hastalık tanısı alan 1.275 hastadan verilerine ulaşılamayan 105 hasta çalışmaya dahil edilmedi. Bin yüz yetmiş hastanın COVID-19 polimeraz zincir reaksiyonu (PCR) testi yapılıp yapılmadığı, pandemi döneminde bilgisayarlı tomografi çekilip çekilmediği ve COVID-19'a bağlı yatış veya yoğun bakım ihtiyacı olup olmadığı, ilaç kullanımları ve komorbiditeleri kaydedildi.

Komorbiditelerden en sık olarak izlenen DM, HT, osteoporoz (OP), kronik hepatit B virüs hastalığı bilgileri verilere eklendi. Hastaların kullandıkları ilaçları, COVID-19 tanısı sırasında bildirilen ilaçları veya en yakın vizitte bildirdikleri ilaç kullanım durumlarından kaydedildi. RA hastalarının seropozitif ve seronegatif olma durumları değerlendirildi.

COVID pozitif hasta grubu, bilgisayarlı tomografide COVID-19 uyumlu bulguları olanlar ve/veya pandemi süresince en az bir kez COVID-19 PCR testi pozitif saptanan hastalar olarak tanımlandı. COVID-19 negatif hastalar ise bir veya daha fazla kez PCR testi yapılıp hiçbirinde pozitiflik saptanmayan hastalar olarak tanımlandı.

Hastalık tanılarına göre altı grup oluşturuldu. 1) Spondiloartrit grubu: ankilozan spondilit (AS), radyografik olmayan aksiyel ve periferik spondiloartrit ve PsA hastalarından oluşmakta. 2) Bağ doku hastalıkları: RA, Scl, sjögren, sistemik lupus eritematozus, farklılaşmamış bağ doku hastalığı, miyozit, juvenil idiyopatik artrit, polimiyalji romatika ve erişkin Still hastalığı. 3) Vaskülitler: Behçet ve diğer vaskülitler. 4) Otoenflamatuvar hastalıklar: FMF. 5) Metabolik hastalıklar: Gut ve psödogut. 6) Diğer: sarkoidoz.

OP tanı kriteri RA veya AS tanılı, uzun süreli (en az 3 ay) ve >5 mg/gün sistemik kortikosteroid kullanımı olanlarda kemik mineral yoğunluğu (KMY) ölçümünde lomber total (L1-4 veya L2-4) veya femur total veya femur boynu KMY ölçümünde "T" değerlerinden herhangi birinin -1 veya daha düşük olması

olarak belirlendi. Diğer romatizmal hastalığı olanlarda, patolojik kırığı olmayan 65 yaş altı hastalarda KMY ölçümünde yukarıda belirtilen "T" değerlerinden herhangi birinin -3 veya daha düşük olması durumunda, patolojik kırığı olmayan 65 yaş üstü hastalarda belirtilen "T" değerlerinden herhangi birinin 2,5 veya daha düşük olması durumunda, patolojik kırığı olan hastalarda ise belirtilen "T" değerlerinden herhangi birinin -1 veya daha düşük olması durumunda OP olarak tanımlandı.

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İstatistiksel Analiz

Çalışmada elde edilen verilerin analizi IBM Statistical Package for Social Sciences versiyon 22 paket programında yapıldı. Değişkenlerin normal dağılıma uygunluğu görsel (histogram ve olasılık grafikleri) ve analitik yöntemlerle (Kolmogorov-Smirnov/Shapiro-Wilk testleri) incelendi. Normal dağılım gösteren devamlı değişkenler ortalama ± standart sapma olarak hesaplandı. Normal dağılım gösteren yaş için Student's t-testi, kategorik değişkenleri karşılaştırmada ise yerine göre ki-kare veya Fisher's exact testi kullanıldı. İlişkilendirme analizlerinde, COVID-19 pozitifliğini ve COVID-19 pozitifliği olanlarda mortaliteyi öngören faktörleri saptamak amacıyla, gruplar arasında farklılık gösteren parametreler bağımsız değişken olarak %95 güven aralığı (GA) ile olasılık oranlarını elde etmek üzere çok değişkenli lojistik regresyon modellerine (enter) yerleştirildi.

Bulgular

Çalışmaya dahil edilen 1.170 hastanın %58,6'sı (686) kadın, %41,4'ü (484) erkekti. Tüm hastaların ortalama yaşı 45,6±15,7 (18-92), kadınların ortalama yaşı 47,8±15,7 (18-92), erkeklerin ortalama yaşı 42,4±16,2 (18-87) saptandı. Hastaların %18,9'unda (221) COVID-19 pozitif (PCR veya tomografi bulguları ile), %20,5'inde (241) COVID-19 PCR negatif tespit edildi. Akciğer bilgisayarlı tomografi çekildiği bilinen 127 hastadan 42'sinde tomografi bulguları COVID-19 ile uyumlu rapor edilmişti. PCR negatif olup, tomografi bulguları ile tanı alan 9 hasta bulunmaktadır. COVID-19 pozitif hastaların hospitalizasyon oranı %13, yoğun bakım yatış oranı %5, tomografi ile saptanmış akciğer tutulum oranı %19 izlendi. Çalışmaya dahil edilen hastalardan %1,2'si (14), COVID-19 pozitif saptanan hastaların %3,2'si (7) hayatını kaybetti. RA hastalarının %74'ü (355) seropozitif, %26'sı (126) seronegatifti.

Tüm hastaların ve COVID-19 pozitif saptananların hastalıklara göre dağılımı, ilaç kullanım durumları ve komorbiditeleri Tablo 1'de gösterilmiştir. En sık görülen hastalık %41,1 ile RA, ikinci sırada %15,9 ile AS ve %9,7 ile radyografik olmayan aksiyel spondiloartritler bulunuyordu. Hastalık grupları içinde COVID-19 geçirme oranlarına bakıldığında en sık FMF (%21,5) ve bağ doku hastalıkları (%21), ardından spondiloartritler (%17) saptandı. İlaç grupları içinde RTX kullananlarda en sık (%33), azatiopürin, sülfasalazin (SLZ) ve mikofenolat mofetil kullananlarda benzer oranlarda (sırasıyla %24, %23, %22) COVID-19 izlendi. Ek hastalıklar açısından bakıldığında, romatizmal hastalığı yanında HT'si olanların en sık COVID-19 geçirme oranına (%27) sahip olduğu görüldü.

Çalışmamızdaki romatolojik hasta popülasyonunda COVID-19 pozitifliği ile cinsiyet, ilaç kullanımı ve ek hastalıklar arasındaki ilişkinin değerlendirmesinde cinsiyet (p=0,04), SLZ kullanımı (p=0,01), HT (p=0,02) ve yaş (p=0,009) ile ilişki saptandı. Ayrıca COVID-19 pozitiflerde tomografi uyumu (p<0,001) ve hospitalizasyon oranı (p=0,009) anlamlı oranda daha yüksek saptandı (Tablo 2).

COVID-19 pozitifliği risk faktörlerinin belirlenmesi için yapılan regresyon analizinde yalnızca SLZ kullanımı 2,1 kat COVID-19 risk artışı ile ilişkili bulundu (Tablo 3).

Çalışmamızdaki COVID-19 pozitif saptanan hasta popülasyonunda ölüm ile cinsiyet, ilaç kullanımı ve ek hastalıklar arasındaki ilişkinin değerlendirmesinde RTX kullanımı (p<0,001), HT (p=0,001) ve yaş (p=0,001) ile ilişki saptandı. Ayrıca ölüm gerçekleşenlerde tomografi uyumu (p=0,005), hospitalizasyon (p<0,001) ve yoğun bakım yatış oranı (p<0,001) anlamlı oranda daha yüksekti (Tablo 2). COVID-19 pozitif hastalarda ölüm risk faktörlerinin belirlenmesi için yapılan regresyon analizinde yalnızca yaş ölüm riski ile ilişkili bulundu. Yaşta 1 birim artış ile ölüm riskinde 1,1 kat artış tespit edildi (Tablo 3).

COVID-19 pozitif olup hayatını kaybeden 7 hastadan 6'sı kadın, 1'ü erkekti; 6'si RA (5'i seropozitf 1'i seronegatif), 1'i gut tanılı idi. Hayatını kaybeden 7 hastanın 1'i RTX, 1'i hidroksiklorokin sülfat (OHQ), 1'i metotreksat (MTX), 1'i MTX+steroid, 1'i leflunomid, 1'i SLZ ve OHQ, 1'i kolşisin kullanıyordu. Hastaların %14'ü (1) DM, %71'i (5) HT, %14'ü (1) OP tanısına sahipti.

Tartışma

Bu çalışmada tek merkezde enflamatuvar romatolojik hastalıkları nedeniyle izlenen hastalarda COVID-19 geçirme durumu, ek hastalıklar ve ilaçların COVID-19 geçirme durumu ve mortalite ile ilişkisinin değerlendirmesi amaçlanmıştır. Çalışmaya dahil edilen hastaların yaklaşık 5'te birinde COVID-19 hastalığı saptandı. Hastalık grupları içinde COVID-19 geçirme oranlarına bakıldığında sıklık sırasına göre FMF, bağ doku hastalıkları ve spondiloartritler izlendi. Romatolojik hastalığı olanlarda SLZ kullanımı COVID-19 geçirme riski ile, COVID-19 pozitiflerde ise yaş ölümle ilişkili bulundu. Türkiye'de COVID-19 hastalığının tüm nüfusa oranı (17.232.066/85.372.377) yaklaşık %20 düzeylerinde olup tek merkez romatoloji hastalarındaki COVID-19 sıklığı ile benzerdir.

Tablo 1: COVID-19 pozitif ve pozitif olmayan hastaların hastalıklara, kullandıkları ilaçlara ve ek hastalıklarına göre dağılımı					
	Tüm hastalar (n=1170) n (%)	**COVID-19 pozitif (n=221) n (%)**	**COVID-19 pozitif olmayan (n=949) n (%)**	**p-değeri**	**%***
Hastalıklar					
RA	481 (41,1)	104 (47,1)	377 (39,7)	**0,05**	22
AS	186 (15,9)	30 (13,6)	156 (16,4)	0,29	16
NrAxSpA	113 (9,7)	20 (9)	93 (9,8)	0,73	18
Behçet	80 (6,8)	11 (5)	69 (7,3)	0,22	14
FMF	77 (6,6)	17 (7,7)	60 (6,3)	0,46	22
Gut	55 (4,7)	6 (2,7)	49 (5,2)	0,12	11
PMR	8 (0,7)	1 (0,5)	7 (0,7)	0,64	12
JIA	4 (0,3)	0 (0)	4 (0,4)	0,33	0
Scl	15 (1,3)	5 (2,3)	10 (1)	0,15	33
Vaskülit	7 (0,6)	1 (0,5)	6 (0,6)	0,75	14
Sjögren	45 (3,8)	9 (4,1)	36 (3,8)	0,84	20
Sarkoidoz	7 (0,6)	2 (0,9)	5 (0,5)	0,51	29
Miyozit	1 (0,1)	0 (0)	1 (0,1)	0,63	0
SLE	51 (4,4)	9 (4,1)	42 (4,4)	0,82	18
Still	2 (0,2)	0 (0)	2 (0,2)	0,49	0
PsA	18 (1,5)	3 (1,4)	15 (1,6)	0,81	17
UBDH	20 (1,7)	3 (1,4)	17 (1,8)	0,65	15
Hastalık grupları					
Spondiloartritler (SpA)	317 (27,1)	53 (24)	264 (28)	0,25	17
Bağ doku hastalıkları (RA+Scl+sj+SLE+ miyozit+UBDH+jia+pmr+still)	627 (54)	131 (59)	496 (52)	0,06	21
Vaskülitler	87 (7,4)	12 (5,4)	75 (8)	0,21	14
Otoenflamatuvar hastalıklar (FMF)	77 (6,7)	17 (7,7)	60 (6)	0,46	21,5
Metabolik hastalıklar (Gut, CPPD)	55 (4,7)	6 (2,7)	49 (5)	0,12	11
Diğer (sarkoidoz)	7 (0,6)	2 (0,9)	5 (0,5)	0,51	29
İlaç kullanımı					
TNFi	154 (13,2)	29 (13,1)	125 (13,2)	0,98	18,8
MTX	288 (24,6)	61 (27,6)	227 (23,9)	0,25	21,2
LFN	161 (13,8)	31 (14)	130 (13,7)	0,89	19,2
OHQ	323 (27,6)	66 (29,9)	257 (27,1)	0,4	20,4
Steroid	397 (33,9)	82 (37,1)	315 (33,2)	0,27	20,6
MMF	13 (1,1)	3 (1,4)	10 (1)	0,7	23,1
AZA	36 (3,1)	9 (4,1)	27 (2,8)	0,34	25
RTX	6 (0,5)	2 (0,9)	4 (0,4)	0,36	33,3
Kolşisin	148 (12,6)	29 (13,1)	119 (12,5)	0,81	19,6
NSAİİ	187 (16)	36 (16,3)	151 (15,9)	0,89	19,2
SLZ	153 (13,1)	36 (16,3)	117 (12,3)	0,12	23,5
Ek hastalıklar					
DM	82 (7)	17 (7,7)	65 (6,8)	0,66	20,7
HT	174 (14,9)	47 (21,3)	127 (13,4)	**0,003**	27
OP	103 (8,8)	22 (10)	81 (8,5)	0,5	21,4
HBV pozitifliği	15 (1,3)	2 (0,9)	13 (1,4)	0,58	13,3

p değeri 0,05 ve 0,05'den küçük olan değerler koyu renk yazılmıştır.
%*: COVID-19 pozitif olanların ait olduğu gruba oranı
RA: Romatoid artrit, AS: Ankilozan spondilit, AZA: Azatioprin, DM: Diabetes mellitus, FMF: Ailevi Akdeniz Ateşi, HBV: Hepatit B virüsü, HT: Hipertansiyon, JIA: Jüvenil idiyopatik artrit, MMF: Mikofenolat mofetil, MTX: Metotreksat, NSAİİ: Non-streoid anti-enflamatuvar ilaçlar, OHQ: Hidroksiklorokin, OP: Osteoporoz, PMR: Polimiyalji romatika, PsA: Psöriatik artrit, RTX: Rituksimab, SLE: Sistemik lupus eritematozus, SLZ: Sülfasalazin, TNFi: Tümör nekroz faktör alfa inhibitörleri, UBDH: Undiferansiye bağ doku hastalığı, COVID-19: Koronavirüs hastalığı-2019, CPPD: Kalsiyum pirofosfat dihidrat, Scl: Skleroderma

Pandeminin başından beri merak konusu olan romatolojik hastalığı olanlarda COVID-19 enfeksiyon oranını genel popülasyonla karşılaştıran birçok çalışma vardır. Pandeminin erken döneminde İspanya'dan retrospektif çok merkezli bir çalışmada, hastaneye başvuran hastalarda referans nüfusa göre COVID-19 prevalansı 1,32 kat yüksek bildirilmiş (16). Güney Kore'den yine salgının erken döneminde 5 aylık sürede COVID PCR + saptanan hastalar içinde romatolojik hastalıkların oranı, morbidite ve mortalitede etkili faktörleri değerlendiren çalışmada romatolojik hastalıkları nedeniyle ≥10 mg steroid alanlarda COVID-19'un sıklığı, ciddiyeti ve mortalitesinde artış ile ilişki gösterilmiştir (17). Yirmi üç çalışmanın dahil edildiği bir meta-analizde romatolojik hastalığı olanlarda COVID-19 göreceli riskinin romatolojik hastalığı olmayanlara göre 1,5 kat,

Tablo 2: COVID-19 pozitif ve negatif saptanan hastaların ve COVID-19 pozitif hastalarda ölüm gerçekleşmeyen ve ölüm gerçekleşenlerin karşılaştırılması

	COVID pozitif (n=221)	COVID negatif (n=241)	p-değeri	COVID pozitif ölüm gerçekleşmeyen (n=214)	COVID pozitif ölen (n=7)	p-değeri
Yaş (ortalama ± SS)	47,4±15,2	43,6±16,3	**0,008**	46,9±14,9	66,6±10,6	**0,001**
Kadın, n (%)	147 (66,5)	138 (57,3)	**0,04**	149 (65,4)	6 (85,7)	0,27
Hospitalizasyon, n (%)	29 (13,1)	2 (0,8)	**0,009**	23 (10,7)	6 (85,7)	**<0,001**
BT uyumu[1], n (%)	42 (19)	0 (0)	**<0,001**	35 (39,7)	7 (100)	**0,005**
YBÜ yatış, n (%)	11 (4,9)	1 (0,4)	0,45	5 (2,3)	6 (85,7)	**<0,001**
TNFi, n (%)	29 (13,1)	39 (16,2)	0,47	29 (13,5)	0 (0)	0,29
MTX, n (%)	61 (27,6)	52 (21,6)	0,13	59 (27,5)	2 (28,5)	0,96
LFN, n (%)	31 (14)	25 (10,4)	0,23	30 (14)	1 (14,3)	0,98
OHQ, n (%)	66 (29,9)	66 (27,4)	0,56	64 (29,9)	2 (28,6)	0,95
Steroid, n (%)	82 (37,1)	71 (29,5)	0,08	80 (37,4)	1 (14,3)	0,21
MMF, n (%)	3 (1,4)	3 (1,2)	0,91	3 (1,4)	0 (0)	0,75
AZA, n (%)	9 (4,1)	10 (4,1)	0,97	8 (3,7)	0 (0)	0,6
RTX, n (%)	2 (0,9)	1 (0,4)	0,5	1 (0,5)	1 (14,3)	**<0,001**
Kolşisin, n (%)	29 (13,1)	33 (13,7)	0,86	28 (13,1)	1 (14,3)	0,93
NSAİİ, n (%)	36 (16,3)	45 (18,7)	0,5	36 (16,8)	0 (0)	0,23
SLZ, n (%)	36 (16,3)	21 (8,7)	**0,01**	35 (16,3)	1 (14,3)	0,88
DM, n (%)	17 (7,7)	12 (4,9)	0,23	16 (7,5)	1 (14,3)	0,51
HT, n (%)	47 21,3)	31 (12,9)	**0,02**	42 (19,6)	5 (71,4)	**0,001**
OP, n (%)	22 (9,9)	21 (8,7)	0,65	21 (9,8)	1 (14,3)	0,7
HBV, n (%)	2 (0,9)	3 (1,2)	0,72	2 (0,9)	0 (0)	0,8

p değeri 0,05'den küçük olan değerler koyu renk yazılmıştır.
[1]BT çekilen hasta sayısı: 88
BT: Bilgisayarlı tomografi, SS: Standart sapma, COVID-19: Koronavirüs hastalığı-2019, YBÜ: Yoğun bakım ünitesi, TNFi: Tümör nekroz faktör inhibitörleri, MTX: Metotreksat, OHQ: Hidroksiklorokin, MMF: Mikofenolat mofetil, AZA: Azatiopürin, RTX: Rituksimab, NSAİİ: Non-streoid anti-enflamatuvar ilaçlar, SLZ: Sülfasalazin, DM: Diabetes mellitus, HT: Hipertansiyon, , OP: Osteoporoz, HBV: Hepatit B virüs enfeksiyonu

Tablo 3: COVID-19 pozitifliği riskini ve COVID-19 pozitiflerde ölüm riskini etkileyen faktörlerin çok değişkenli lojistik regresyon analiz sonuçları

	COVID pozitifliği riski	p-değeri	COVID pozitiflerde ölüm riski	p-değeri
	RR (%95 GA)		RR (%95 GA)	
Cinsiyet (kadın-erkek)	1,3 (0,9-2)	0,13	-	-
Steroid kullanımı	1,2 (0,8-1,8)	0,37	-	-
Sülfasalazin kullanımı	**2,1 (1,2-3,8)**	**0,01**	-	-
Hipertansiyon	1,4 (0,8-2,4)	0,26	4,2 (0,6-26)	0,13
Yaş	1 (0,9-1,02)	0,20	**1,1 (1,006-1,2)**	**0,009**
RTX kullanımı	-	-	16,2 (0,7-366)	0,08

p değeri 0,05'den küçük olan parametreler koyu renk yazılmıştır.
RR: Risk oranı ile gösterilen tahmini rölatif risk, COVID-19: Koronavirüs hastalığı-2019, RTX: Rituksimab, GA: Güven aralığı

ölüm riskinin 1,7 kat arttığı bildirilmiştir (18). Bu meta-analizde karşılaştırmalı değerlendirilmenin yapıldığı 46 çalışmanın 15'inde risk artışı bildirilirken, 27'sinde fark gösterilememiş ve 4'ünde azalmış risk bildirilmiştir (18). Seksen üç çalışmanın alındığı bir diğer metaanalizde romatolojik hastalıklarda COVID-19 prevalansının bölgelere göre değiştiği vurgulanmıştır (19). Bu metaanalizde yaş, cinsiyet, sigara ve komorbiditeler romatoloji hasta popülasyonunda COVID-19 riski ile ilişkili bulunmamıştır. Bizim çalışmamızda ise yalnızca SLZ kullanımı COVID-19 pozitifliği açısından artmış risk ile ilişkili bulunmuştur.

Ülkemizden tek merkez çocuk romatoloji kliniğinde takipli hastalarda COVID-19 seyrini değerlendiren bir çalışmada, COVID-19 prevalansı yaklaşık %2 bildirilmiş olup erişkin romatoloji hastalarından oldukça düşük olduğu görülmektedir (20). Pandeminin başında ülkemizde yapılan çok merkezli bir çalışmada, COVID-19 pozitif saptanan 165 romatoloji hastası değerlendirilmiş. Çalışma popülasyonunun %14,5'i ayaktan izlenirken, %85,5'inde hastane yatışı gerekmiş ve hastaların mortalite oranı %10 saptanmış. Komorbiditeler ve steroid kullanımı daha kötü sonlanımla ilişkili bulunurken, biyolojik DMARD'lar kötü sonlanımla ilişkili bulunmamış (21). Yine ülkemizden 1.500 COVID-19 pozitif hastanın dahil edildiği çok merkezli bir çalışmada, hospitalize edilen hastalardaki mortalite oranı %4,5 olarak bildirilmiş (22).

Çalışmamızdaki COVID-19 hastalarının cinsiyet, hastalık tipi, hospitalizasyon ve ölüm oranları COVID-Global Romatoloji Birliği (23) veritabanın, Xu ve ark.'nın (24) metaanalizi ve Türkiye'den Esatoglu ve ark.'nın (21) çalışmaları ile karşılaştırıldığında kadın oranının her üç veri tabanında yüksek (sırasıyla %66, %76, %64 ve %58) hospitalizasyon (%13, %33, %56 ve %86) ve ölüm oranlarının (%3,2, %6,7, %7 ve %10) daha düşük saptandığı görülmektedir. Bu fark hasta sayısı, komorbidite oranları, çok merkezli veri tabanlarında yanlılık ve çalışmaların bir kısmında yalnızca hastaneye başvuran hastaların alınmış olmasına bağlanabilir. COVID-19 saptanan romatoloji hastalarının oranlarına bakıldığında ise toplumdaki sıklıkları ile paralel şekilde çalışmamızda ve diğer üç veri tabanında RA ilk sırada yer almaktadır.

Romatolojik hastalıklarda genel popülasyona göre COVID-19 ilişkili ölüm oranlarında değişiklik olup olmadığı pandeminin başından beri merak ve birçok çalışmanın konusu olmuştur. COVID-Global Romatoloji Birliği'ne dahil 81 ülkenin Haziran 2020'ye kadar COVID-19 verilerine göre 3.729 romatoloji hastasının ölüm riski yaş, komorbidite ve ≥10 mg prednizon eşdeğeri kullanımı ile ilişkili bulunmuştur. Bizim çalışmamızda da benzer şekilde yaş ve komorbiditelerden HT varlığı mortalite ile ilişkili iken, çok değişkenli değerlendirmede yalnızca yaş ölümle ilişkili saptanmıştır.

Steroidlerin COVID-19'un hiperenflamasyon fazında mekanik ventilasyon ihtiyacı ve ölüm riskinde azalmaya neden olsa da, kronik kullanımlarının romatolojik hastalıklarda şiddetli COVID-19 riskini artırabileceği gösterilmiştir (25). Benzer şekilde orta-şiddetli COVID-19 hastalarında yapılan retrospektif çalışmalarla da kısa süreli 0,5-1 mg/kg metilprednizolon kullanımının yoğun bakım, mekanik ventilatör ihtiyacı ve mortaliteyi anlamlı şekilde azalttığı ve hastane kalış süresini kısalttığı gösterilmiştir (26,27). Erken dönem şiddetli COVID-19 hastalarında, 3 gün 250 mg/gün pulse steroid etkisini değerlendiren tek kör, randomize kontrollü bir çalışmada mortalite oranının anlamlı olarak azaldığı (sırasıyla %5,9 ve %42,9; p<0,001) ve hayatta kalım süresinin daha uzun olduğu bildirildi (log-rank testi: p<0,001; risk oranı 0,293, %95 GA: 0,154-0,556) (28). Yedi randomize çalışmanın alındığı prospektif bir metaanalizde de kritik hastalığı olan COVID-19 hastalarında sistemik steroid kullanımının plasebo veya standart tedaviye göre 28 günlük mortaliteyi azalttığı bildirilmiştir (29). Diğer taraftan 43 çalışmanın dahil edildiği, steroid kolunda 19.426 ve standart tedavi kolunda 77.426 hastanın bulunduğu bir metaanalizde mortalite oranları sırasıyla %14,2 (2.749) ve %7,1 (5.459) olup steroid ile 2,17 kat ölüm riskinde artış (%95 GA: 2,0690-2,2820) bildirilmiştir (30). Bu risk artışında steroidin, COVID-19 erken replikasyon döneminde virüs klirensini azaltması ve sekonder enfeksiyonlarda artış ile ilişkili olabileceği vurgulanmıştır. Pandemi döneminde Amerikan Romatoloji Cemiyeti enflamatuvar artrit hastalarında gerekli durumlarda kortikosteroidlerin düşük dozlarda (<10 mg/gün) başlanmasını önermiştir (14).

Romatolojik hastalıkla ilişkili faktörlerden hastalık aktivitesi, RTX ve SLZ kullanımının ölüm riski ile ilişkili olduğu gösterilmiş (23). Hedefe yönelik veya biyolojik ilaç kullanan 2.869 RA hastasında ölüm oranı %5,5 ve janus kinaz (JAK) inhibitörü veya RTX kullanımı tümör nekroz faktörü inhibitörü kullanımına göre COVID-19 kötü sonlanımları açısından daha riskli bulunmuştur (31). Ancak JAK inhibitörü tofasitinib ve barisitinibin oksijen ihtiyacı hızla artan hastalarda steroide eklenmesinin klinikte düzelme ile ilişkili olabileceği gösterildi (32,33). RTX ile ilgili, son bir yıl içinde RTX tedavisi aldığı bilinen 76 romatoloji hastasının değerlendirildiği bir çalışmada hastalardan 13 (%17,1)'ünde COVID-19 tespit edilmiş ve bu hastaların hastaneye yatarak tedavi oranları %61,5 ve mortalite oranları %23,1 oranında yüksek bulunmuştur (34). İspanya'dan yayınlanan bir çalışmada 72 RTX kullanan hastadan 7'sinin (%9,7) ağır COVID-19 pnömonisi nedeniyle hastanede yatarak tedavi alması gerektiği, bu hastaların mortalite oranı %42,8 ve diğer ilaçlarla karşılaştırıldığında RTX'ın hospitalizasyon açısından 12,9 kat risk artışı ile ilişkili olduğu bildirilmiştir (35). RTX B hücre hedefli bir tedavi olup, diğer hastalıklarda da B hücre azaltıcı tedavilerin romatolojik hastalıklar dışında kullanımında da COVID-19 mortalitesi ile ilişkili olduğu gösterilmiştir (36). Bizim çalışmamızda da ilaçlar içinde yalnızca RTX, COVID-19 geçirenlerde ölen ve ölüm gerçekleşmeyen romatolojik hasta oranları açısından anlamlı farklıydı.

Çalışmamızdaki tek merkezde takipli romatoloji hastalarından COVID-19 pozitif saptananların ölüm oranı %3,2 iken Türkiye genelinde COVID-19 saptananlar içinde ölüm oranı (102.174/17.232.066) %0,59 (https://covid19.saglik.gov.tr), tüm dünyada ise (7,035,337/774,771,942) %0,9 idi (https://data.who.int/dashboards/covid19/deaths?m49=001&tn=o).

Çalışmanın Kısıtlılıkları

COVID-19 saptanan romatolojik hastalarda ölüm oranı görece yüksek saptanmış olsa da, yaş-cinsiyet ve komorbiditeler açısından eşleştirilmiş bir grupla karşılaştıramamış olmak çalışmamızın eksik yönlerindendir. Ayrıca asemptomatik COVID-19 enfeksiyonu geçirmiş olanlar, antikor testi ile tanı alanlar veya semptomatik olsa bile sağlık kuruluşuna başvurup tetkik edilmemiş olan hastaların çalışmamıza alınamamış olması da çalışmamızın eksik yönlerindendir.

Romatoloji hastalarında COVID-19 sıklığı, romatolojik hastalıkların ve kullanılan ilaçların prognoza ve mortaliteye etkisi ile ilgili çalışmaların çoğunluğu pandeminin ilk bir yılı içinde yapılmıştır. Bu çalışma ise pandemi dönemi boyunca COVID-19 pozitifliğini değerlendirmesi nedeniyle hem daha geniş bir zaman dilimini değerlendirmenin avantajlarını hem de değişen varyantlar ve aşılanmanın etkisine bağlı değişen enfeksiyon sıklığına bağlı karşılaştırma dezavantajlarına sahiptir. COVID-19 pandemisinin farklı zaman dilimlerinde farklı bölgelerdeki verileri karşılaştırmak, ülke ve bölgelerin korunma önlemleri, virüs varyantları, aşı etkisi, veri kaynakları ve güvenilirliği gibi nedenlerle dikkat gerektirmektedir.

Hastaneye başvuran hastalar değil, tek merkezde tanı almış tüm enflamatuvar romatolojik hastalığı olan hastaların COVID-19 açısından değerlendirilmesi ise çalışmamızın güçlü yönlerindendir.

Sonuç

Sonuçta, kısıtlılıklar nedeniyle sonuçları yorumlamak güç olmakla birlikte, tek merkezde takipli romatoloji hastalarında COVID-19 riski için SLZ kullanımı, mortaliteyi öngörmede yaş en önemli risk faktörü olarak bulunmuştur. Romatoloji hastalarında COVID-19'a bağlı ölüm oranı Türkiye geneliyle karşılaştırıldığında görece yüksek saptanmış olup literatürdeki verilerle benzerdir.

Etik

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Hasta Onayı: Geriye dönük çalışma olması nedeniyle hasta onamı alınmamıştır.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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CERRAHİ TIP BİLİMLERİ / SURGICAL MEDICAL SCIENCES

Over Kanseri Tanısı Almış Hastaların Semptomlarının ve İyilik Halinin Değerlendirilmesi

Symptom Management in Patients Diagnosed with Ovarian Cancer

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Öz

Amaç: Bu çalışma ile Ankara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda over kanseri tanısı almış olan hastaların, tedavi süreçlerinde semptomlarının belirlenmesi ve standardize ölçeklerle iyilik hallerinin ortaya konulması amaçlanmıştır.

Gereç ve Yöntem: Bu araştırma, tanımlayıcı tipte olup Ankara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda over kanseri tanısı almış olan hastalarda gerçekleştirilmiştir. Araştırma kriterlerine uygun ve çalışmaya katılmayı kabul eden kadınlara aydınlatılmış onam formu okutulup, imzalatıldıktan sonra "Tanıtıcı Özellikler Formu" ve "Nightingale Semptom Değerlendirme Ölçeği (NSDÖ)" anketleri kullanılarak veriler yüz yüze olarak toplanmıştır.

Bulgular: Çalışmaya over kanseri tanısı almış 100 kadın dahil edilmiştir. NSDÖ toplam skorlarına, meslek, doğum sayısı, yaşanılan yer, sosyal güvence, birlikte yaşanılan kişiler, soy geçmişinde kanser öyküsü olma durumunun anlamlı olarak etki ettiği bulunmuştur ($p<0,05$). Alt boyut puan ortalamaları incelendiğinde psikolojik iyilik hali puan ortalamasının, fiziksel iyilik hali puan ortalaması ve sosyal iyilik hali puan ortalamasına göre daha yüksek olduğu tespit edilmiştir.

Sonuç: Multidisipliner bir ekip anlayışıyla, her bireye özgü geliştirilen bakımın iyileştirici ve önleyici etkileri sayesinde over kanserli kadınların iyilik hallerine katkıda bulunulabilir. Fiziksel, sosyal ve psikolojik sağlık unsurlarının iyileştirilmesi için çalışmamızda saptadığımız faktörlerin göz önünde bulundurulması yararlı olacaktır.

Anahtar Kelimeler: Over, kanser, semptom, iyilik hali

Abstract

Objective: The aim of this study was to determine the symptoms of patients diagnosed with ovarian cancer in the Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine and to determine their well-being using standardized scales.

Materials and Method: This descriptive study was conducted in patients diagnosed with ovarian cancer at Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology. After the informed consent form was read and signed by the women who met the research criteria and agreed to participate in the study, the data were collected face-to-face using the "Descriptive Characteristics Form" and "Nightingale Symptom Assessment Scale (N-SAS)" questionnaires.

Results: The study included 100 women diagnosed with ovarian cancer. It was found that occupation, number of births, place of residence, social security, cohabitants, and having a family history of cancer had a significant effect on the total scores of the N-SAS ($p<0.05$). When the sub-dimension mean scores were examined, it was found that the mean score of psychological well-being was higher than the mean score of physical well-being and social well-being.

Conclusion: A multidisciplinary team approach can contribute to the well-being of women with ovarian cancer through the curative and preventive effects of care developed specifically for each individual. In order to improve physical, social and psychological health factors, it would be useful to consider the factors we identified in our study.

Keywords: Ovary, cancer, symptoms, well-being

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Giriş

Jinekolojik kanserler kadın üreme organlarının malign hastalıklarıdır. Dünyada kadınlarda en sık görülen jinekolojik kanserler, serviks, endometrium ve over kanserleridir (1,2). Over kanseri bir veya her iki overi etkileyebilir. Görülme sıklığı yaygın değildir, ancak sıklıkla ileri evreye kadar tespit edilemediğinden mortalite oranı yüksektir (2,3). Tedaviye bağlı görülen semptomlar hastaların yaşam kalitesini olumsuz etkilemektedir (4). Semptomlar; bireyin biyopsikososyal fonksiyonları, duyuları veya kognitif değişiklikleri yansıttıkları çok boyutlu, kompleks ve subjektif fenomenlerdir (4,5).

Semptom yönetimi ile tedaviye bağlı gelişen semptomların oluşmasını engellemek veya ortaya çıkanları kontrol altına almak önemlidir (4,5). Hastaların yaşadığı semptomların çok boyutlu olarak ele alınması semptom kontrolünün sağlanması, yaşam kalitesi için önem sağlamaktadır (5-8). Bu araştırma, over kanseri tanısı alan hastaların tedavi süreçlerinde yaşadıkları semptomların belirlenmesini, standardize ölçekler kullanılarak fiziksel, sosyal ve psikolojik iyilik hallerinin ölçülmesi ve bunları etkileyen faktörlerin belirlenmesini amaçlamaktadır. Bu sayede hastaların iyilik hallerinin düzeltilmesine yönelik öneriler geliştirilmesi de amaçlanmıştır.

Gereç ve Yöntem

Tanımlayıcı tipteki bu araştırmanın evrenini 01.12.2021 ve 01.02.2022 tarihleri arasında Ankara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı Jinekolojik Onkoloji Polikliniği'ne başvuran ve over kanseri tanısı alan 100 kadın oluşturmaktadır. Araştırmaya dahil edilme kriterleri, araştırmaya katılmayı kabul eden, 18 yaş ve üzeri primer tanısı over kanseri olan kadınlardır. Araştırmaya dahil edilmeme kriterleri ise nörolojik ve psikiyatrik bozukluğu olan kadınlardır.

Araştırmanın Değişkenleri

Over kanseri tanısı alan kadınların semptomları bağımlı değişkeni, over kanseri tanısı alan kadınların sosyo-demografik özellikleri ise araştırmanın bağımsız değişkenlerini oluşturmaktadır.

Verilerin Toplanması

Araştırma kriterlerine uygun olan ve araştırmaya katılmaya kabul eden kadınlara, araştırmanın amacı ve içeriği hakkında araştırmacı tarafından açıklamalar yapılmıştır. Ardından, koronavirüs hastalığı-2019 algoritmasına uygun şekilde (önlük, tıbbi maske, siperlik ve gözlük) giyinen araştırmacılar, sosyal mesafe kuralına uyarak "Aydınlatılmış Onam Formu" ve "Bilgilendirilmiş Gönüllü Olur Formu" okutulup, imzalatıldıktan sonra "Tanıtıcı Özellikler Formu" ve "Nightingale Semptom Değerlendirme Ölçeği (NSDÖ)" anket soruları katılımcılar tarafından cevaplanmıştır. Anket sorularının cevaplanması yaklaşık 15-20 dakika sürmüştür.

Tanıtıcı Özellikler Formu

Tanıtıcı Özellikler Formu, araştırmacılar tarafından literatür bilgisi doğrultusunda ve alanında uzman olan 7 uzmandan (1 doktor, 6 hemşire akademisyen) uzman görüşleri alınarak hazırlanmış olup, kadınların yaş, cinsiyet, meslek, hastalık bilgisi gibi tanıtıcı özelliklerini içeren sorulardan oluşan bir formdur.

NSDÖ

NSDÖ 2009 yılında kanser tanısı almış hastalar için Adnan Aydıner ve Gülbeyaz Can tarafından geliştirilmiştir. Ölçek; fiziksel iyilik hali (FizİH), sosyal iyilik hali (SoİH), psikolojik iyilik hali (PsİH) olmak üzere üç alt boyutu içeren toplam 38 maddeden oluşmaktadır. Ölçeğin Cronbach alfa değerleri ise; SoİHα=0,87, FizİHα=0,81, PsİHα=0,93'tür.

Araştırma Etiği

Araştırma için Ankara Üniversitesi Rektörlüğü Etik Kurulu Başkanlığı'ndan 01/11/2021 tarihinde 16/183 karar sayısı ile onay alınmıştır. Araştırma kriterlerine uygun ve çalışmaya katılmayı kabul eden kadınlara aydınlatılmış onam formu okutulup, imzalatıldıktan sonra "Tanıtıcı Özellikler Formu ve NSDÖ" anketleri katılımcılar tarafından cevaplanmıştır.

İstatistiksel Analiz

Veriler, bilgisayar ortamında SPSS paket programının 22.0 sürümü ile değerlendirilmiştir. Tanımlayıcı veriler sayı, yüzde ve ortalama ile gösterilmiştir. Verilerin değerlendirilmesinde sürekli değişkenler Student's t-testi, kategorik değişkenler ki-kare testi ile değerlendirilmiş ve Pearson korelasyon analizi kullanılmıştır. Sonuçların anlamlılık seviyesi ve güven aralığı %95 ($p<0,05$) olarak belirlenmiştir.

Bulgular

Çalışmamıza katılan kadınların yaş ortalaması 61,09±1,07 idi. Hastaların %69'unun evli, %46'sının ilkokul mezunu olduğu, %78'inin çalışmadığı belirlenmiştir. %49'unun eşi ile birlikte ve %45'inin il merkezinde yaşadığı, %66'sının İç Anadolu Bölgesi'nde doğduğu, %61'inin gelirinin giderine eşit ve %97'sinin sosyal güvencesinin olduğu bulunmuştur. Katılımcıların gebelik sayısı ortalaması 3,26±0,19, doğum sayısı ortalaması 2,53±0,15 ve menopoz yaşı ortalaması 46,99±0,66 olarak belirlenmiştir. Hastaların %22'sinin soygeçmişinde kanser öyküsü olduğu görülmüştür (Tablo 1). Hastaların %69'unun 3. evre over kanseri olduğu, %88'inin ameliyat öyküsü bulunduğu, %99'unun radyoterapi almadığı, %91'inin kemoterapi aldığı, %54'ünün kronik hastalığının olmadığı, %59'unun ek bir ilaç kullanmadığı bulunmuştur (Tablo 2). Hastalarda fiziksel yan etkiler incelendiğinde en çok; %92'sinin kendini yorgun

Tablo 1: Hastaların sosyo-demografik özellikleri (n=100)	
Tanıtıcı özellikler	**n (%)**
Medeni durum	
Evli	69 (69)
Bekar	31 (31)
Eğitim durumu	
Okuryazar	6 (6)
İlkokul	46 (46)
Ortaokul	6 (6)
Lise	26 (26)
Üniversite	8 (4)
Okuryazar değil	4 (4)
Meslek	
Çalışan	22 (22)
Çalışmayan	78 (78)
Doğduğu coğrafi bölge	
İç Anadolu	66 (66)
Marmara	3 (3)
Doğu Anadolu	3 (3)
Güneydoğu Anadolu	2 (2)
Ege	10 (10)
Akdeniz	6 (6)
Karadeniz	9 (9)
Diğer (yurtdışı)	1 (1)
Gelir durumu	
Gelir gidere eşit	61 (61)
Gelir giderden az	23 (23)
Gelir giderden fazla	16 (16)
Evde birlikte yaşanılan kişiler	
Yalnız	11 (11)
Eş	49 (49)
Çocuklar	15 (15)
Eş ve çocuklar	23 (23)
Diğer (akraba)	2 (2)
Yaşanılan yer	
İl	45 (45)
İlçe	33 (33)
Köy	22 (22)
Sosyal güvence	
Var	97 (97)
Yok	3 (3)
Soygeçmişte kanser öyküsü	
Var	22 (22)
Yok	78 (78)

hissettiği, %84'ünün uyku düzeninde bozulma olduğu, %79'unun dışarı çıkmak istemediği, %77'sinin iştahında azalma olduğu ve %77'sinin eklem/kas ağrıları yaşadığı bulunmuştur. Hastaların yaşadığı sosyal sorunlar incelendiğinde %88'inin kirpik ve kaşının döküldüğü, %84'ünün saçının döküldüğü ve %79'unun deride kuruluğun arttığı, pul pul döküntülerinin olduğu belirlenmiştir. Hastaların yaşadığı psikolojik sorunlar incelendiğinde ise %88'inin daha duyarlı/hassas olduğu, %85'inin günlük ihtiyaçlarını karşılamada zorlandığı, %84'ünün cinselliğe ilgisinin azaldığı görülmüştür (Tablo 3). Hastaların toplam NSDÖ puanı 1,59±0,65 olduğu, alt boyut FizİH puanının 1,42±0,71, SoİH puanının 1,62±0,70 ve PsİH puanının 1,74±0,82 olduğu saptanmıştır (Tablo 4). NSDÖ toplam ve alt boyut

Tablo 2: Kadınların yaş, gebelik sayısı, doğum sayısı, menopoz yaşı, ilk ve son skor ölçek sonucuna göre dağılımı	
Değişkenler	**Ortalama ± SS**
Yaş ortalaması	61,09±1,07
Gebelik sayısı	3,26±0,19
Doğum sayısı	2,53±0,15
Menopoz yaşı	46,99±0,66
SS: Standart sapma	

Tablo 3: Hastaların tıbbi özellikleri	
Tıbbi özellikler	**n (%)**
Over kanseri evresi	
Evre I	1 (1)
Evre II	8 (8)
Evre III	69 (69)
Evre IV	22 (22)
Ameliyat öyküsü	
Var	88 (88)
Yok	12 (12)
Radyoterapi alma	
Evet	1 (1)
Hayır	99 (99)
Kemoterapi alma	
Evet	91 (91)
Hayır	9 (9)
Ek hastalık	
Var	46 (46)
Yok	54 (54)
Sürekli kullanılan ilaç	
Var	41 (41)
Yok	59 (59)

puanları ile sosyo-demografik özellikler karşılaştırıldığında, FizİH alt boyutunda yaşanılan yer açısından anlamlı farklılık olduğu bulunmuştur (p<0,05). SoİH alt boyutunda meslek, doğum sayısı, yaşanılan yer ve sosyal güvence açısından anlamlı farklılık vardır (p<0,05). PsİH alt boyutunda yaş, medeni durum, birlikte yaşanılan kişiler, yaşanılan yer, soy geçmişinde kanser öyküsü olma açısından anlamlı farklılık olduğu görülmüştür (p<0,05). Medeni durum ve yaşanılan coğrafi bölgeye göre ölçek toplam puan ortalaması arasında anlamlı farklılık olduğu (p<0,05) görülmüştür.

Tartışma

Bu çalışma ile over kanserli kadınlarda psikolojik, sosyal ve fiziksel iyilik halleri ve etkileyen faktörler belirlenmiştir. Buna göre medeni durum ve yaşanılan coğrafi bölge kadının sosyal ve fiziksel iyilik halini etkilemektedir ve bu bulgumuz diğer çalışmaların sonuçlarını desteklemektedir (9,10). Ayrıca çalışmamıza katılan kadınların en çok yaşadığı fiziksel semptomlar; yorgunluk, uyku düzeninde bozulma, dışarıya çıkmak istememe olarak belirlenmiştir. Arslan ve Bölükbaş'ın (11) çalışmasında en sık görülen fiziksel semptomlar; halsizlik

Tablo 4: Hastaların fiziksel, sosyal ve psikososyal semptom dağılımları

Semptomlar	Evet	Hayır
	n (%)	n (%)
Fiziksel Semptomlar		
Kendimi yorgun hissettim	92 (92)	8 (8)
Bulantım oldu	73 (73)	7 (7)
Dışarıya çıkmak istemedim	79 (79)	21 (21)
İştahım azaldı	77 (77)	23 (23)
Yediklerimin tadını farklı algıladım	62 (62)	38 (38)
Eklem/kaslarımda ağrım oldu	77 (77)	23 (23)
El ve ayaklarımda uyuşma/karıncalanma oldu	75 (75)	25 (25)
Kabız oldum	61 (61)	39 (39)
Ağzımda/diş etlerimde hassasiyet oldu	66 (66)	34 (34)
Uyku düzenim bozuldu	84 (84)	16 (16)
Grip benzeri şikayetlerim oldu	64 (64)	36 (36)
Kusmam oldu	63 (63)	37 (37)
Ağzımda yara oldu	52 (52)	48 (48)
Dikkatimi yoğunlaştırmakta zorlandım	73 (73)	27 (27)
Boğazımda ağrı oldu	46 (46)	54 (54)
Lokmalarımı yutmakta zorlandım	49 (49)	51 (51)
Titrememem oldu	65 (65)	35 (35)
İshal oldum	64 (64)	36 (36)
Ateşim 38 °C üstüne çıktı	67 (67)	33 (33)
Hıçkırığım oldu	48 (48)	52 (52)
Sosyal semptomlar		
Saçlarım döküldü	84 (84)	16 (16)
Kirpiklerim ve kaşlarım döküldü	88 (88)	12 (12)
Unutkanlığım arttı	69 (69)	31 (31)
Derimde kuruluk arttı, pul pul döküntüler oldu	79 (79)	21 (21)
Avuçlarımda ve ayak tabanlarımda kızarıklık oldu	69 (69)	31 (31)
Deri rengim koyulaştı	56 (56)	44 (44)
Kaşıntım oldu	59 (59)	41 (41)
Tırnaklarımın görünümü/yapısı değişti	63 (63)	37 (37)
Psikolojik semptomlar		
Cinselliğe ilgim azaldı	84 (84)	16 (16)
Daha duyarlı/hassas oldum	87 (87)	13 (13)
Sosyal yaşantımdan uzaklaştım	69 (69)	31 (31)
Kendimi içime kapanmış hissettim	80 (80)	20 (20)
Geleceğe yönelik endişelerim oldu	83 (83)	17 (17)
Daha çabuk sinirlenir oldum	74 (74)	26 (26)
Aile/arkadaş ilişkilerim bozuldu	66 (66)	34 (34)
Dışarıda yürüyüş yapmakta zorlandım	78 (78)	22 (22)
Günlük işlerimi sürdürmede zorlandım	80 (80)	20 (20)
Günlük ihtiyaçlarımı karşılamada zorlandım	85 (85)	15 (15)

Tablo 5: Hastaların NSDÖ toplam puanlarının dağılımı

NSDÖ puanları	Ortalama ± SS
FizİH	1,42±0,71
SoİH	1,62±0,70
PsİH	1,74±0,82
Genel iyilik hali	1,59±0,65

NSDÖ: Nightingale Semptom Değerlendirme Ölçeği, FizİH: Fiziksel iyilik hali, SoİH: Sosyal iyilik hali, PsİH: Psikolojik iyilik hali, SS: Standart sapma

ve yorgunluk olarak bildirilmiştir. Sarı Şıra'nın (5) çalışmasında en sık görülen fiziksel semptomlar; halsizlik, yorgunluk ve bulantı olduğu belirtilmiştir. Üstündağ'ın (12) çalışmasında ise bu semptomlar; yorgunluk, bulantı, dışarıya çıkmak istememe olarak belirtilmiştir. Literatürdeki bu bulgular bizim çalışmamız ile benzerdir. Çalışmamızda kadınların bu süreçte en çok yaşadığı sosyal semptomlar ise; kirpik ve kaş dökülmesi, saç dökülmesi ve derinin kuruyup pul pul dökülmesi en az yaşanan sosyal semptom ise deri renginin koyulaşmasıdır. Sarı Şıra'nın (5), Arslan ve Bölükbaş'ın (11), çalışmalarında hastaların en çok yaşadığı semptom saç dökülmesi olarak belirtilmiştir. Coolbrandt ve ark. (13), çalışmasında ise en çok saç dökülmesi ve deride değişiklik yaşandığı saptanmıştır. Üstündağ'ın (12) çalışmasında ise kirpik kaş ve saç dökülmesi en çok yaşanan semptom olarak bildirilmiştir. Araştırma sonuçlarımız literatür ile benzerlik göstermektedir. Çalışmamızda kadınların psikolojik iyilik halinin değerlendirilmesinde çoğunlukla daha duyarlı/hassas oldukları ve günlük ihtiyaçlarını karşılamada zorlandıkları saptanmıştır. Çalışmamızda kadınların psikolojik iyilik hali puan ortalamaları daha yüksek bulunmuştur. Bu alt boyutun diğer alt boyut puan ortalamalarından daha yüksek olması hiç şüphesiz ki kadınların bu süreçte sadece iş yaşamındaki rolünün yanı sıra diğer alanlarda olan görev ve rolleri ile ilişkilendirebilir. NSDÖ skorları ile hastaların yaş, medeni durum, doğum sayısı, yaşanılan yer, kimle yaşadığı, sosyal güvence ve ailede kanser öyküsü olma açısından anlamlı bir ilişki olduğu saptanmıştır (p<0,005). Yaş ortalamasının artmasıyla birlikte hastaların fiziksel semptomlardan etkilenme düzeyi de artmakta olup, genel skorun azalmakta olduğu görülmüştür (10,14). Çalışmamızda evli olanların genel iyilik hallerinin bekar olanlara göre iyi olması daha fazla sosyal destek almalarına bağlı olabileceği düşünülmektedir. Arslan ve Bölükbaş (11) ve Eom ve ark.'nın (15) yapmış oldukları çalışmalarda medeni durumu evli olanların yaşam kalitelerinin daha yüksek olduğunu bildirmişlerdir. Üstündağ (12), çalışmasında ise bu durum tam tersi olarak bildirilmiş olup, bekar olanların psikolojik iyilik halinin ve yaşam kalitesinin evli hastalardan daha kötü olduğu bildirilmiştir. Araştırma sonuçlarımız literatür ile benzerlik göstermektedir. Yaşanılan yer parametresinde köyde yaşayanların genel iyilik hallerinin il ve ilçede yaşayanlardan daha yüksek olduğu bulunmuştur. Bu durumun şehir hayatının stresinden uzak bir yaşam sürdürmeyle ilgili olabileceği düşünülmektedir. Pınar ve ark.'nın (16), hastaların birlikte yaşadığı kişilerin yaşam kalitelerini etkilediğini bildirmişlerdir. Bizim çalışmamızda eşi ve çocukları ile yaşayanların diğer akrabaları ile yaşayan gruba göre genel iyilik halleri arasında farklı olduğu saptanmıştır. Bu durumun aynı zamanda kişinin doğum sayısıyla da ilgili olabileceği düşünülmektedir, çocuk sayısının fazla olması genel iyilik puan ortalamasını da etkilemektedir. Hastaların bu süreçte sosyal güvencesinin olması özellikle tedavi hizmetlerinden yararlanmasını kolaylaştırıp, genel iyilik halini etkilemektedir.

Sonuç

Over kanser tanısı alan hastalar, tedavi sürecinde birçok fiziksel, sosyal ve psikolojik semptomla karşılaşabilmektedir.

Bu semptomların etkili bir şekilde yönetimi, hastaların tedavi sürecindeki yaşam kalitelerini artırmada kritik bir rol oynamaktadır. Özellikle yorgunluk, uyku bozuklukları, günlük ihtiyaçları karşılamada zorluk ve cinsel ilgide azalma gibi semptomlar hakkında hasta ve ailesinin önceden bilgilendirilmesi ve baş etme yöntemleri konusunda eğitim verilmesi büyük önem taşımaktadır.

Gelişebilecek semptomların ve bunların yönetim şekillerinin hasta ve ailesi tarafından bilinmesi, kişilerin daha güvende hissetmelerini sağlamakta ve hastanın tedavi sürecine daha aktif katılımını teşvik etmektedir. Multidisipliner bir ekip anlayışıyla, her bireye özgü geliştirilen bakımın iyileştirici ve önleyici etkileri sayesinde over kanserli kadınların iyilik halleri desteklenebilir.

Fiziksel, sosyal ve psikolojik sağlık unsurları bir arada ele alındığında, hastaların genel yaşam kaliteleri korunabilir ve iyileştirilebilir. Ayrıca, literatürde bu konuda yeterli çalışma bulunmadığı için, daha geniş örneklem gruplarına sahip araştırmalarla yeni ve daha kapsamlı sonuçların elde edilmesi önerilmektedir.

Etik

Etik Kurul Onayı: Araştırma için Ankara Üniversitesi Rektörlüğü Etik Kurulu Başkanlığı'ndan (karar no.: 16/183, tarih: 01.11.2021) onay alınmıştır.

Hasta Onayı: Araştırma kriterlerine uygun ve çalışmaya katılmayı kabul eden kadınlara "Aydınlatılmış Onam Formu" okutulup, imzalatıldıktan sonra "Tanıtıcı Özellikler Anketi" ve "Cinsel Yaşam Kalitesi Ölçeği (Kadın)" anketleri kullanılarak veriler yüz yüze olarak toplanmıştır.

Dipnotlar

Yazarlık Katkıları

Konsept: C.A., Ö.Ö., Dizayn: C.A., Ö.Ö., Veri Toplama veya İşleme: C.A., Z.Ö., G.A., E.G., H.Y., Analiz veya Yorumlama: G.A., Y.E.Ş., Ç.Ö., S.T. Literatür Arama: C.A., Z.Ö., G.A., Ö.Ö., Yazan: Z.Ö.

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Analysis of Emergency Internal Medicine Hospitalization after the Earthquake in Türkiye: Demographic and Clinical Results of Victims

Türkiye'deki Deprem Sonrası Acil Dahiliye Servisi Yatışlarının Analizi: Mağdurların Demografik ve Klinik Sonuçları

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Abstract

Objectives: On February 6, 2023, a devastating earthquake struck the southeastern part of Türkiye that affected eleven major cities. Thousands of people lost their lives, and many were buried under collapsed buildings. The aim of this study is to examine the demographic characteristics, clinical results, laboratory findings and injuries of the victims who applied to the emergency internal medicine service after the earthquake.

Materials and Methods: In this study, medical records of 60 patients with crush syndrome who applied to Ankara Bilkent City Hospital Emergency Department of Internal Medicine after the earthquake were evaluated retrospectively through the system.

Results: 56.67% of the patients were male, the mean age was 37.35, the mean duration of stay under the rubble was 28.39 hours, and 40 (66.67%) patients had extremity trauma. Twenty-two patients (36.67%) had fasciotomy and 15 (25%) had amputation. Various complications developed in patients; 36 acute kidney injury (AKI) (60%) and 15 (25%) wound infections were detected. Hemodialysis was applied to 32 patients (53.33%) due to AKI. AKI was detected in 17 of the patients who underwent fasciotomy, and wound infection was observed in 9 of them. Wound infection was detected in 13 of the patients with AKI. Mortality developed in 3 patients. In the comparison between patients with and without fasciotomy, it was found that there was a significant difference in terms of length of hospitalization, number of transfusions, AKI, wound infection, hemodialysis, myoglobin on admission value. In patients with acute renal failure; wound infection, hemodialysis, transfusion rates, myoglobin value >1000 (µg/L) at admission and urea at admission, creatinine at admission, creatine kinase rate at admission were higher.

Conclusion: Rapid determination of demographic characteristics, laboratory findings and clinical results of earthquake patients are critical for the development of future disaster preparedness, response and recovery policies.

Keywords: Earthquake, crush syndrome, acute kidney injury, Türkiye

Öz

Amaç: 6 Şubat 2023'te Türkiye'nin güneydoğu bölgesini etkileyen yıkıcı bir deprem meydana geldi ve on bir büyük şehri etkiledi. Binlerce insan hayatını kaybetti ve birçok kişi yıkılan binaların altında kaldı. Bu çalışmanın amacı, deprem sonrasında acil dahiliye servislerine başvuran mağdurların demografik özelliklerini, klinik sonuçlarını, laboratuvar bulgularını ve yaralanmalarını incelemektir.

Gereç ve Yöntem: Bu çalışmada, deprem sonrası Ankara Bilkent Şehir Hastanesi Dahiliye Acil Servisi'ne başvuran ve crush sendromu olan 60 hastanın tıbbi kayıtları sistem üzerinden retrospektif olarak değerlendirildi.

Bulgular: Hastaların %56,67'si erkek, ortalama yaş 37,35, enkaz altında kalma süresi ortalama 28,39 saat ve 40 hastada (%66,67) ekstremite travması vardı. Yirmi iki hastaya (%36,67) fasiyotomi ve 15 hastaya (%25) ampütasyon yapıldı. Hastalarda çeşitli komplikasyonlar gelişti; 36 akut böbrek hasarı (ABH) (%60) ve 15 (%25) yara enfeksiyonu tespit edildi. ABH nedeniyle 32 hastaya (%53,33) hemodiyaliz uygulandı. Fasiyotomi

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yapılan hastaların 17'sinde ABH ve 9'unda yara enfeksiyonu gözlendi. ABH olan hastaların 13'ünde yara enfeksiyonu tespit edildi. Üç hastada mortalite gelişti.

Sonuç: Deprem hastalarının demografik özelliklerinin, laboratuvar bulgularının ve klinik sonuçlarının hızlı bir şekilde belirlenmesi, gelecekteki afet hazırlığı, müdahale ve iyileşme politikalarının geliştirilmesi açısından kritiktir.

Anahtar Kelimeler: Deprem, crush sendromu, akut böbrek hasarı, Türkiye

Introduction

On February 6, 2023, the two most devastating earthquakes of the last century occurred in Türkiye. In the early hours of February 6, Türkiye's Kahramanmaraş province experienced its first earthquake measuring 7.7 on the Richter scale. A second earthquake with a magnitude of 7.6 occurred in the same region. More than 16 million people were affected by earthquakes in 11 provinces including Adana, Adıyaman, Diyarbakır, Gaziantep, Hatay, Kahramanmaraş, Kilis, Osmaniye and Şanlıurfa (1). Crush syndrome (CS) can develop as a result of crush injuries due to natural disasters such as earthquakes. Various complications occur as a result of CS. As a result of these complications, mortality and morbidity may develop (2). CS may occur as a result of necrosis in cells secondary to skeletal muscle ischemia and mechanical force (3). The severity of complications is proportional to the amount of injured body part and muscle. As a result of these complications, electrolyte imbalance, metabolic acidosis, acute kidney injury (AKI) may develop (4). In addition to cardiac involvement, patients may also have respiratory failure and pulmonary involvement due to pneumothorax, hemothorax and pulmonary contusion. Acute respiratory distress syndrome is one of the most important pulmonary complications (5,6).

Acute compartment syndrome (ACS) is another life-threatening complication that may require emergency surgery in patients who remained under debris. Pathophysiologically, microvascular circulation and capillary permeability are impaired and ischemia and edema develop in the myofascial compartment. As a result, there is an increase in intracompartmental pressure due to edema and mass increase (7-9).

The literature lacks information on emergency internal medicine services, demographics, laboratory and clinical outcomes among disaster victims (10-12). The aim of this study is to examine the demographic characteristics, laboratory findings, clinical results and injuries of the victims who applied to the emergency internal medicine service after the earthquake. Research findings can contribute to the development of preparedness, response and recovery policies for future disasters.

Materials and Methods

In this study, the medical records of 60 patients with CS hospitalized in the Emergency Internal Medicine Department of Ankara Bilkent City Hospital after the earthquake were evaluated retrospectively through the system. Ethics committee approval for the study was obtained from the Ankara Bilkent City Hospital No. 2 Clinical Research Ethics Committee (approval no.: E2-23-3705, date: 15.03.2023). All patients had crush injuries. Patients with at least one of the systemic complications such as AKI, electrolyte imbalance, rhabdomyolysis [5-fold increase in creatine kinase (CK) values], hypovolemic shock and ACS after crush injuries were evaluated as CS. Similar to the literature, indications for fasciotomy were determined as bullae, pain, ecchymosis, absence of pulse in the extremity, and increased intracompartmental pressure.

Age, length of hospital stay, fasciotomy and amputation surgeries, development of ACS, length of stay under rubble, body parts injured as a result of trauma, need for hemodialysis, laboratory values at admission; Blood gas parameters, Creatinine, urea, lactate dehydrogenase, myoglobin, electrolytes and CK parameters were evaluated. Fasciotomy, amputation, time spent under rubble, mortality, and laboratory parameters in patients with AKI were evaluated.

In our study, 22 patients underwent fasciotomy and 15 patients underwent amputation. Fasciotomy and amputation surgery were not performed simultaneously in any of the patients during their hospitalization. The discharge time was taken into account when evaluating the clinical and laboratory findings.

Statistical Analysis

Statistical analysis was made by Statistical Package for Social Sciences version 25. Normality of variables was analyzed by histogram graphics and Kolmogorov-Smirnov test. In the descriptive findings section of the statistical analysis, categorical variables were presented as number and percentage, and continuous variables were presented as mean ± standard deviation (SD) for normally distributed data and median (minimum, maximum) for non-normally distributed data. Continuous variables were expressed either as mean ± SD or as median and minimum-maximum values according to normality. Categorical variables were compared with the chi-square test. The Mann-Whitney U test was used when evaluating non-normally distributed (non-parametric) variables between two groups. Spearman correlation test was used in the analysis of the measurement data with each other. Cases with a p-value below 0.05 were considered as statistically significant results.

Results

In this study, we presented 60 adult CS patients, 34 males and 26 females, aged 18-85 years, who were admitted to our hospital. All patients had crush injuries. The mean duration of being under the rubble was 28.39±32.32 hours. The mean length of hospitalization was 24.58±8.07 days. The distribution and demographic characteristics of the patients according to myoglobin values and time spent under the rubble are shown in Table 1.

According to the areas exposed to trauma; 40 patients (66.67%) for extremity, 4 for hip (6.67%), 7 for vertebra (11.67%), 11 for thorax (18.33%), 1 for cranial (1.67%) were determined in the study. Twenty-two (36.67%) patients underwent fasciotomy and 15 (25%) patients underwent amputation surgery. Various complications developed in patients; 36 patients with AKI (60%), 15 with wound infection (25%) were identified. Thirty-two patients underwent hemodialysis (53.33%) due to AKI. Mortality developed in 3 patients (5%) due to respiratory failure and related complications. Patients distribution by trauma site, operation performed, hemodialysis and mortality was shown in Table 2.

In the comparison between patients with and without fasciotomy, it was found that there was a significant difference in terms of length of hospitalization, number of transfusions, AKI, wound infection, hemodialysis, myoglobin on admission value. Accordingly, length of hospitalization, number of transfusions, AKI, wound infection, hemodialysis rate were found to be higher in patients with fasciotomy ($p<0.05$). Also, the rate of patients with a myoglobin on admission value >1000 (µg/L) were found to be higher (Tables 3, 4).

In the comparison between patients with and without amputation, it was observed that there was a significant difference in terms of length of hospitalization, urea value on admission, creatinine value on admission ($p<0.05$). Accordingly, while length of hospitalization was higher in patients with amputation, urea on admission and creatinine on admission values were lower (Tables 5, 6).

Table 1: Demographic characteristics of patients and their distribution values

		n	%
Gender	Male	34	(56.67)
	Female	26	(43.33)
*Age		37.35±15.13	34.5 (18-85)
*Time under the rubble (h)		28.39±32.32	15 (1-144)
*Length of stay in internal medicine clinic (day)		24.58±8.07	27 (3-36)

n: Number of patients, %: Proportion in the whole population, *n is replaced by mean ± SD, % is replaced by median (minimum-maximum)
SD: Standard deviation

Table 2: Patients distribution by trauma site, operation performed, hemodialysis and mortality

	n	%
Trauma area		
Extremity	40	(66.67)
Hip	4	(6.67)
Vertebra	7	(11.67)
Thorax	11	(18.33)
Cranial	1	(1.67)
Operation performed		
Fasciotomy	22	(36.67)
Amputation	15	(25.00)
Complications		
Acute renal failure	36	(60.00)
Wound infection	15	(25.00)
Hemodialysis and mortality		
Hemodialysis	32	(53.33)
Mortality	3	(5.00)

n: Number of patients, %: Proportion in the whole population

Table 3: Distribution of number of hemodialysis, complications, mortality and laboratory values according to fasciotomy

		Fasciotomy				p-value
		No		Yes		
		n	%	n	%	
Myoglobin on admission (µg/L)	<1000	18	(48.65)	2	(9.09)	**0.002**
	>1000	19	(51.35)	20	(90.91)	
Acute renal failure		19	(50.00)	17	(77.27)	**0.038**
Wound infection		6	(15.79)	9	(40.91)	**0.030**
Hemodialysis		15	(39.47)	17	(77.27)	**0.005**
Mortality		1	(2.63)	2	(9.09)	0.269

Mann-Whitney U test/chi-square test
Bold values: Statistically significant parameters (p<0.005)
n: Number of patients, %: Proportion in the whole population

Table 4: Comparison of demographic characteristics of patients, length of stay in internal medicine clinic (day), number of transfusions, complications and laboratory values according to fasciotomy

	Fasciotomy				p-value
	No		Yes		
	Mean ± SD	Median (Min.-Max.)	Mean ± SD	Median (Min.-Max.)	
Age	39.53±16.74	37.5 (19-85)	33.59±11.21	33 (18-66)	0.225
Time under the rubble (h)	31.2±32.46	22 (1-144)	23.55±32.23	12 (4-144)	0.222
Length of stay in internal medicine clinic (day)	22.11±8.72	23.5 (3-36)	28.86±4.31	30 (17-36)	**0.004**
Transfusions	3.32±7.09	0 (0-30)	15.91±23.07	8.5 (0-80)	**0.003**
On Admission					
Urea (mg/dL)	89.22±85.76	50.07 (12.84-393)	92.83±57.15	90.95 (14.9-241)	0.421
Creatinine (mg/dL)	2.57±2.87	0.99 (0.23-10.65)	3.38±1.93	3.64 (0.35-7.11)	0.092
Creatine kinase (U/L)	20314.45±26733.5	8380.5 (508-114208)	43802.05±70486.02	9324 (340-287071)	0.311

Mann-Whitney U test
Bold values: Statistically significant parameters (p<0.005)
SD: Standard deviation, Min.: Minimum, Max.: Maximum

Table 5: Distribution of complications. Hemodialysis, mortality and laboratory values according to amputation

		Amputation				p-value
		No		Yes		
		n	%	n	%	
Mortality		2	(4.44)	1	(6.67)	0.732
Acute renal failure		29	(64.44)	7	(46.67)	0.224
Hemodialysis		26	(57.78)	6	(40.00)	0.232
Wound infection		10	(22.22)	5	(33.33)	0.389
Myoglobin on admission (µg/L)	<1000	17	(38.64)	3	(20.00)	0.188
	>1000	27	(61.36)	12	(80.00)	

Mann-Whitney U test/chi-square test
n: Number of patients, %: Proportion in the whole population

Table 6: Comparison of demographic characteristics of patients, length of stay in internal medicine clinic, number of transfusions, complications and laboratory values according to amputation

	Amputation				p-value
	No		Yes		
	Mean ± SD	Median	Mean ± SD	Median	
Age	37.51±16.15	34 (18-85)	36.87±12.02	35 (19-66)	0.745
Time under the rubble (h)	29.06±35.85	14 (1-144)	26.4±18.92	24 (2-60)	0.489
Length of stay in internal medicine clinic (day)	22.89±8.15	25 (3-36)	29.67±5.38	30 (14-36)	**0.004**
Transfusions	6.69±15.83	1 (0-80)	11.67±16.79	3 (0-60)	0.21
Urea (mg/dL)	104.39±81.28	102.7 (12.84-393)	49.01±33.49	40.6 (12.84-128)	**0.016**
Creatinine (mg/dL)	3.26±2.73	2.99 (0.27-10.65)	1.69±1.63	0.67 (0.23-4.92)	**0.036**
Creatine kinase (U/L)	29026.27±52533.28	8258 (340-287071)	28627.47±34880.41	15486 (1182-114208)	0.361

Mann-Whitney U test
Bold values: Statistically significant parameters (p<0.005)
SD: Standard deviation

In the comparison made according to the development of AKI; it was found that there was a significant difference in terms of wound infection, hemodialysis, myoglobin on admission, number of transfusions, urea on admission, creatinine on admission, CK on admission, lactate dehydrogenase on admission, potassium on admission, pH on admission, HCO3 on admission, calcium on admission values (p<0.05). Accordingly, in patients with AKI; wound infection, hemodialysis, transfusion rates, the rate of patients with a myoglobin on admission value >1000 (µg/L), and urea on admission, creatinine on admission, CK on admission values were higher. Comparison and distribution of demographic characteristics of CS patients, time spent under the rubble, length of hospitalization, number of traumatized extremities, number of hemodialysis, number of transfusions, wound infection, mortality and laboratory values according to AKI is shown in Tables 7, 8.

Wound infection was more common in patients with AKI. AKI was more common in patients who underwent fasciotomy, unlike amputation.

Discussion

Various complications are seen in earthquake victims with CS. Few studies in the literature contain detailed data on patients with CS. Due to the lack of complete and accurate data during the earthquake, adequate studies on CS could not be carried out. After the 1988 Armenian earthquake and the Hanshin-Awaji earthquake, the hospital records of the patients with CS could not be kept fully and accurately (13-16). Unlike the literature, in our study, the clinical and laboratory data of the patients who applied to our hospital due to the need for further examination and treatment were recorded in detail. In our study, it was found that the age range of patients with ACS and crush injuries was similar to the literature (17,18).

In the literature, intracompartmental pressure measurement is recommended for the diagnosis of ACS. In this way, it has been stated that the development of ACS can be observed in the early period and surgical intervention can be applied at the

Table 7: Distribution of number of hemodialysis, complications, surgeries, mortality and laboratory values according to AKI

	Acute renal failure				p-value
	No		Yes		
	n	%	n	%	
Fasciotomy	5	(20.83)	17	(47.22)	**0.038**
Amputation	8	(33.33)	7	(19.44)	0.224
Wound infection	2	(8.33)	13	(36.11)	**0.015**
Hemodialysis	1	(4.17)	31	(86.11)	**<0.001**
Myoglobin on admission (µg/L)	<1000 12	(52.17)	8	(22.22)	**0.018**
	>1000 11	(47.83)	28	(77.78)	
Mortality	0	(0.00)	3	(8.33)	0.147

Mann-Whitney U test/chi-square test
Bold values: Statistically significant parameters (p<0.005)
n: Number of patients, %: Proportion in the whole population
AKI: Acute kidney injury

Table 8: Comparison of demographic characteristics of patients, time spent under the rubble, length of stay in internal medicine clinic, number of traumatized extremities, number of hemodialysis, number of transfusions and laboratory values according to AKI

	Acute renal failure				p-value
	No		Yes		
	Mean ± SD	Median (Min.-Max.)	Mean ± SD	Median (Min.-Max.)	
Age	35.75±12.13	33.5 (19-66)	38.42±16.92	35 (18-85)	0.803
Time under the rubble (h)	38.44±37.05	36 (1-144)	21.69±27.26	12.5 (1-144)	0.108
Length of stay in internal medicine clinic (day)	24.04±8.59	26.5 (3-35)	24.94±7.8	27 (10-36)	0.757
Total number of traumatized extremities	1.77±0.83	2 (1-4)	1.59±0.69	2 (1-4)	0.514
Transfusions	2.17±5.76	0 (0-26)	11.78±19.39	3.5 (0-80)	**0.001**
On admission					
Urea (mg/dL)	32.14±11.54	30.6 (14.9-51.36)	132.12±71.89	124.5 (20-393)	**<0.001**
Creatinine (mg/dL)	0.63±0.18	0.64 (0.24-1)	4.45±2.18	4 (1.17-10.65)	**<0.001**
Creatine kinase (U/L)	14335±19415.44	3950.5 (508-76368)	38837.58±58851.85	10646 (340-287071)	**0.030**
pH	7.46±0.05	7.46 (7.38-7.57)	7.38±0.1	7.4 (7-7.54)	**<0.001**
HCO_3 (mmol/L)	25.45±3.02	25.9 (18.3-30.1)	20.34±5.6	21.2 (6.6-29.1)	**<0.001**
Calcium (mg/dL)	8.43±0.44	8.43 (7.66-9.53)	8.16±0.69	8.17 (6.88-10.32)	**0.039**
Potassium (mEq/L)	4.12±0.47	4.15 (3.1-5.2)	4.92±1.25	4.57 (3.2-7.8)	**0.017**

Mann-Whitney U test
Bold values: Statistically significant parameters (p<0.005)
AKI: Acute kidney injury, SD: Standard deviation, Min.: Minimum, Max.: Maximum

right time (19). One of the main problem which encountered in the earthquake zone is the pressure measurement. Therefore, in areas with earthquake risk, portable compartment pressure measurement devices can prevent fasciotomy and amputation operations in patients whose surgical indications cannot be determined exactly.

Fasciotomy was performed on 22 crush injury patients. Similar to the study of Safari et al. (20), no significant relationship was found between age, gender, and duration of being under the rubble in terms of fasciotomy. Unlike Huang et al. (21) our study found no significant relationship between CK level and fasciotomy. We recommend that CK level not be used as a guide when determining patients undergoing fasciotomy. In our study, similar to the literature, wound infections were significantly higher in patients with fasciotomy. It is recommended to avoid unnecessary fasciotomy surgeries in crush injury patients whose indications are not established due to the increased risk of infection (22,23). In the literature, the amputation rate after fasciotomy ranges from 11% to 38.7% (24-27). In our study, amputation was not performed in patients who underwent fasciotomy. Hyperkalemia in patients with CS causes severe cardiac arrhythmias and may result in mortality if patients are not treated (28,29). In our study, no mortality due to hyperkalemia was observed due to close follow-up and rapid hemodialysis application.

Another important complication in patients with crush injury is AKI due to rhabdomyolysis. In our study, we found that increased CK values significantly increased the possibility of developing AKI. 60% of the patients with elevated CK levels had AKI. This rate was 0.5% for the Iran earthquake, 3.3% for the Hanshin-Awaji earthquake and 2.7% for the Marmara earthquake (16,30,31). The rate was %18.3 in the study by Kantarcı et al. (32) after the 1999 Marmara earthquake. We thought that the reason for the high rate in our study compared to the literature was that our hospital was a tertiary level hospital and patients who required advanced treatment in terms of kidney replacement were referred to our hospital.

The reason for this was that hydration was started in the early period as soon as the survivors were removed from the rubble, and the awareness of health care professionals about treatment increased due to previous earthquakes. Contrary to the literature, we found a low mortality rate in patients with CS (8.33%). In similar studies in the literature, mortality rates were 40% in the Iran earthquake, 24.7% in the Hanshin-Awaji earthquake, and 15.2% in the Marmara earthquake, respectively. We thought that the reason for this was good management of complications and a multidisciplinary approach (16,29,30).

In our study, wound infection was more common in patients with AKI. Similar to the study of Zhang et al. (33), we found that wound infection is an important complication after fasciotomy. We thought that toxic metabolites, acidosis, and electrolyte imbalances contributed to the development of wound infections, especially in patients with AKI. We thought that the high incidence of wound infection was due to renal failure and

acidosis as a complication of fasciotomy. In the study of Childs et al. (34), similar to our study, it was found that the development of AKI increased the risk of infection. The number of transfusions was found to be significantly higher in patients who underwent fasciotomy and developed AKI ($p<0.001$). Similarly, it has been determined in the literature that the need for transfusion will increase due to the complications of CS. In addition, in the study of Kazancioglu et al. (35) it was stated that obtaining sufficient amounts of blood products is important in patients with CS. We recommend starting adequate blood supply immediately after the earthquake.

Rapid determination of demographic characteristics, laboratory findings and clinical results of earthquake patients are critical for the development of future disaster preparedness, response and recovery policies.

Study Limitations

The limitations of our study were that the patients were not followed up after discharge and the number of patients was low. In addition, the short follow-up period of the patients and the fact that they were followed only in the internal medicine clinic were also limitations.

Conclusion

We found that fasciotomy and amputation prolonged hospital stay in earthquake victims with CS. In addition, healthcare professionals should be more careful in terms of wound infection in patients with AKI.

As a result of this study, demographic information, laboratory findings, epidemiological information about treatment and outcome will be valuable in improving disaster relief.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Ankara Bilkent City Hospital No. 2 Clinical Research Ethics Committee (approval no.: E2-23-3705, date: 15.03.2023).

Informed Consent: Informed consent not available due to retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A., Concept: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A., Design: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A., Data Collection and/ or Processing: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A., Analysis and/or Interpretation: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A., Literature Search: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A., Writing: O.Z., B.G., M.G., M.D.G., F.Ş.S., M.D., E.S.Ş., O.İ., E.C.Y., F.D., İ.A.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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TEMEL TIP BİLİMLERİ / BASIC MEDICAL SCIENCES

Ankara Üniversitesi Tıp Fakültesi'nin Parlayan Yıldızlarından, Türkiye'de Çocuk Hematoloji ve Onkoloji'nin Kurucusu: Prof. Dr. Ayhan (Okçuoğlu) Çavdar

One of the Shining Stars of Ankara University Faculty of Medicine, the Founder of Pediatric Hematology and Oncology in Türkiye: Prof. Dr. Ayhan (Okçuoğlu) Çavdar

Hülya Öztürk Karataş

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Öz

Amaç: İbni Haldun, "İnsanlar doğar, büyür, yaşlanır ve ölür" der, bu döngüde insanoğlu, var olduğu andan itibaren yaşamını anlamlandırabilme adına eylemlerde bulunur, tarihsel süreçte kendi var oluş öyküsünü oluşturmaya çalışır. Çalışmamızda Ayhan Çavdar ve yaşamı, bilimsel ve toplumsal çalışmalarını tıp tarihi inceleme yöntemlerine göre araştırmak amaçlanmıştır.

Gereç ve Yöntem: Prof. Dr. Ayhan Çavdar'ın biyografisi ve bilime olan katkısı yaşayan yakınlarıyla yapılan söyleşiler, aile arşivine ait kayıtlar ile Türkiye Büyük Millet Meclisi zabıt ve tutanaklar arşivleri ve gazeteler kullanılarak nitel araştırma yöntemlerine göre incelenmiştir.

Bulgular: Prof. Dr. Ayhan O. Çavdar dünyadaki varlığını, mesleksel veya toplumsal çalışmaları ve sergilediği duruşu ile onurlu kişiliği sayesinde sağlamlaştırmıştır. Sağlık alanına verdiği katkıların yanında meslek etiği konusundaki hassasiyeti, sağlıkta çalışan pek çok insana bakış açısı sağlamış, kendisinin de başarılarının taçlanmasına ve isminin hala anılır olmasına sebebiyet vermiştir. Prof. Dr. Ayhan Çavdar, meslek yaşantısı dışında bilimin pek çok alanında katkı vermeye çalışmış, Türkiye Bilimler Akademisi'nin kurucu başkanlığı, Türk Hematoloji Derneği ve Atatürkçü Düşünce Derneği kurucu üyeliklerini sürdürmüş, topluma fayda amaçlı her türlü eylemde canla başla kendisini ortaya koymuştur.

Sonuç: Prof. Dr. Ayhan O. Çavdar'ı tanıyabilmek, bilim insanları ve genç hekim adaylarına yeni pencereler açabileceği gibi onurlu bir yaşamın yansımalarını da gözler önüne seren yönüyle de bilim insanlarına örnek olacak pek çok özelliği barındırmaktadır.

Anahtar Kelimeler: Ayhan Okçuoğlu Çavdar, Ankara Üniversitesi Tıp Fakültesi, biyografi, çocuk hematoloji ve onkolojisi

Abstract

Objectives: Ibn Haldun states, "People are born, grow, age, and die", in this cycle, humanity takes actions to make sense of their lives from the moment of existence, striving to create its own story of existence throughout history. In our study, the life of Ayhan Çavdar and his scientific and social endeavors are intended to be investigated according to the methods of medical history research.

Materials and Methods: The biography of Prof. Dr. Çavdar and his contributions to science were examined using qualitative research methods, including interviews with his close relatives, records from the family archives, as well as records from the TBMM-*Grand National Assembly of Türkiye* and newspapers.

Results: Prof. Dr. Çavdar solidified his existence in the world through his professional or social endeavors and the honorable personality he displayed. In addition to his contributions to the field of health, his sensitivity to professional ethics has provided a perspective to many individuals working in healthcare, contributing to his own success and the perpetuation of his name. Prof. Dr. Çavdar has endeavored to contribute to various fields of science beyond his professional career, serving as the founding president of the Turkish Academy of Sciences, and maintaining memberships in the Turkish Hematology Society and the Atatürk Thought Society, demonstrating his dedication to any action aimed at benefiting society.

Conclusion: Understanding Çavdar not only has the potential to open new windows for scientists and young medical professionals but also serves as an example to scientists due to the many qualities that reflect an honorable life.

Keywords: Ayhan Okcuoglu Cavdar, Ankara University Faculty of Medicine, biography, pediatric hematology and oncology

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Giriş

Prof. Dr. Ayhan Çavdar, Türkiye'nin önde gelen akademisyenlerinden biri olarak, bilim dünyasına yaptığı önemli katkılarla tanınmaktadır. Onun uzun yıllara yayılan akademik kariyeri, sayısız araştırma ve yayınla zenginleşmiş, birçok öğrenci ve araştırmacıya ilham kaynağı olmuştur. Çeşitli alanlarda gerçekleştirdiği çalışmalarla hem ulusal hem de uluslararası arenada saygın bir konuma sahip olan Prof. Dr. Çavdar, bilime olan adanmışlığı ve özverili çalışmalarıyla dikkat çekmektedir.

Ankara Üniversitesi Tıp Fakültesi'nin (cumhuriyetin ilk tıp fakültesi) efsane hocalarından Prof. Dr. Ayhan Okçuoğlu Çavdar, 12 Ağustos 1930 tarihinde Adana'da dünyaya gelmiştir. Beş çocuklu bir ailede doğan Çavdar, ailenin dördüncü çocuğudur (1,2).

Ayhan O. Çavdar, Ankara Üniversitesi Tıp Fakültesi'nde 1947 yılından 1953 yılına kadar eğitim görmüştür. Tıp okuduğu yıllardan itibaren kan hastalıklarıyla ilgilenmiş ve bu alan onu çok etkilemiştir. 1953'te çocuk kliniğinde asistanlık eğitimine başlamış ve 1956'da tamamlamıştır. Asistanlık bitirme tezi konusunu "trombositler" üzerine seçmiştir. Bu konu üzerine çalışmalarını Amerika'da St. Louis şehrindeki Washington Üniversitesi'ne giderek geliştirmiş ve tamamlamıştır. Ülkeye dönüşünün ardından 1961 yılında doçent olan Ayhan Çavdar, genellikle çalışmalarını seçerken ülkemizde ihtiyaç duyulan alanları takip etmiş ve yaşadığı ülkenin sorunlarına ilişkin çalışmalar yapmayı önceliklemiştir (3).

Bu çalışma, Prof. Dr. Ayhan Çavdar'ın hayatını, akademik kariyerini ve bilim dünyasına yaptığı katkıları ayrıntılı bir şekilde incelemeyi amaçlamaktadır. Onun bilimsel yolculuğu ve elde ettiği başarılar, sadece akademik çevrelerde değil, aynı zamanda genel toplumda da büyük bir takdirle karşılanmaktadır. Makalemizin amacı, akademik dünyada iz bırakmış bir bilim insanı olan Ayhan Çavdar'ın yaşamını ve çalışmalarını kayıt altına alarak bu mirası geleceğe daha geniş kitlelere tanıtarak genç akademisyenlere ve öğrencilere ilham kaynağı oluşmasını sağlamaktır.

Gereç ve Yöntem

Geçmişte yaşamış ya da henüz hayatta olan kişilerin geçmişini konu edinen biyografiler tarih yazımında nitel araştırma yöntemleri içerisinde yer alır. Bir olgu veya olayı kendi doğasına uygun bir şekilde ve derinlemesine inceleyen nitel araştırma yönteminin kullandığı veri toplama araçları içerisinde çoklu veri toplama araçlarının kullanılmasıyla ortaya konulan biyografi yazılarında bir hayatın canlandırılması, yazan tarafından yeniden sunulması sağlanır. Burada kişinin yakınları ile görüşmeler yanında, gözlem ve dokümantasyon belge ve formları kullanılarak veriler toplanır ve analiz edilir. Aile bireyleri ile görüşülmesi biyografi yazılarında büyük önem taşımaktadır. Biyografisi yazılan kişiyi daha iyi tanıyabilmek adına gerçekleştirilen görüşmelerde, özellikle birinci derece yakınları ve arkadaşlarından görüşmeyi kabul eden ve katkı vermek isteyen kişiler tercih edilir. Görüşmeyi kabul eden kişilerin izlenimleri, düşünceleri, görüşleri biyografi yazımında önemli birincil bilgiler sağlaması açısından önemlidir. Arşiv materyalleri ve belgeler ya da araştırmacının canlı tanıklarla yaptığı röportajlar kullanılarak biyografisi yazılan bireyin yaşamındaki önemli dönemler, kesitler halinde biyografi yazımında verilir (4).

Prof. Dr. Ayhan Çavdar'ın biyografisinin kaleme alındığı bu çalışma, tıp tarihi incelemeleri yöntemlerinden nitel araştırma deseni kullanılarak hazırlanmıştır. Türkiye Büyük Millet Meclisi'ne (TBMM) ait belgeler ve dönemin gazete ile dergileri, Ekim 2023 ve Şubat 2024 tarihleri arasında yazar tarafından tasnif edilerek çalışmada kullanılmıştır. Ayrıca makale ve kitap gibi ikincil kaynaklar da araştırma sürecinde yararlanılan diğer kaynaklar arasında yer almıştır.

Çalışmada, Prof. Dr. Ayhan Çavdar'ın hayatı, kişilik özellikleri, bilimsel yaşamı boyunca ortaya koyduğu çalışmalar ve Türkiye Bilimler Akademisi (TÜBA) başkanlığı dönemi, tıp tarihi araştırma yazılarında kullanılan biyografi inceleme yöntemleri doğrultusunda tarafsızlık ölçütüyle değerlendirilmiştir. Yazıda, biyografi yazımı için gerekli olan yalın ve anlaşılır bir üslup kullanılmaya çalışılmış; dönemin gazeteleri ve TBMM'ye ait dokümanlar, çalışmanın konusunu oluşturan dönemler esas alınarak incelenmiştir. Belgeler tasnif edildikten sonra ilgili bulunan belgeler, tahlil ve tenkit süreçlerinin ardından metin içerisinde kronolojik bir sıralamayla kullanılmıştır. Ayhan Çavdar'ın aile ve yakınlarıyla yapılan görüşmeler ve arşiv belgelerinin tarama, tasnif, tahlil ve tenkit süreçleri 8 aylık bir çalışmayla gerçekleştirilmiştir.

Aile ile görüşmelerden önce, aileye yöneltilecek sorular; hayatı, kişisel özellikleri, aile ve çalışma hayatı, TÜBA dönemi başkanlığı gibi kategoriler altında hazırlanmış, form aileye iletilmiş ve görüşme için randevu talep edilmiştir. Sözel rıza ve randevunun oluşturulmasının ardından, ailenin kendi evinde gerçekleştirilen iki yüz yüze görüşme, toplamda 5-6 saat sürmüş; sorulara verilen yanıtlar not alınarak görüşme sonlandırılmıştır. Görüşmelerde alınan notlar transkribe edildikten sonra aileye e-posta yoluyla iletilmiş ve yeniden teyit alındıktan sonra, metin içerisinde ailenin Prof. Dr. Ayhan Çavdar hakkında verdikleri bilgiler kullanılmıştır.

Ailesi dışında, çalışma arkadaşları ve öğrencilerine aileden alınan telefon numaraları aracılığıyla ulaşılmış; bilgilendirme sonrasında kendilerinden Prof. Dr. Ayhan Çavdar'ı anlatan yazılar talep edilmiştir. Konu ile ilgilenen ve rıza gösteren kişiler yazılarını yazarın e-posta adresine iletmiş ve kullanım izni vermişlerdir. Ayhan Çavdar'ın eski çalışma arkadaşı olup vefat eden hocaların mektupları ise aile tarafından tarafımıza ulaştırılmış ve metinde kullanılmıştır.

Bulgular

Ayhan Okçuoğlu Çavdar'ın Yaşam Öyküsü, Eğitim Hayatı ve Çalışma Yılları

Prof. Dr. Ayhan Çavdar'ın annesi Bingöl ili Kiğı bölgesinden Bedia Çavdar, babası ise Elazığ eşrafından Mustafa Nuri Okçuoğlu'dur. Babası, I. Dünya Savaşı sonrasında Darülfünun İstanbul Üniversitesi Hukuk Fakültesi'ndeki eğitimini tamamlamış, Anadolu'nun pek çok yerinde görev yapmış, Yargıtay İkinci Hukuk Dairesi üyeliği ve TBMM'de iki dönem milletvekilliği görevlerini yerine getirmiştir. Milletvekilliği için adaylığını eşinin memleketi Bingöl'den koyan M. Nuri Bey, IX. Dönem (1950-1954) ve XI. Dönem (1957-1960) yıllarında iki dönem boyunca Bingöl'de milletvekili olarak Türkiye Büyük Millet Meclisi'nde görev yapmıştır (1-3,5,6). Dört kardeşi olan Ayhan O. Çavdar, babasının görevi dolayısıyla çocuk yaşlarından itibaren oldukça fazla seyahat etmiş, ülkenin pek çok yerinde bulunmuş ve eğitim hayatını tamamlamaya çalışmıştır. Lise eğitimini İstanbul Erenköy Kız Lisesi'nde tamamlayan Ayhan Çavdar, meslek seçimi sırasında bir ağabeyini dönemin bulaşıcı hastalıklarından kaybetmesi ve insanlara yardım hislerinin kuvveti dolayısıyla tıbba yönelmiş ve verdiği pek çok röportajda konuyla ilgili hassasiyetini dile getirmiştir (1,2,5). Ayhan Çavdar, 1967 yılında Ankara Barosu'ndan Avukat Arif Çavdar ile evlenmiş ve vefat ettiği döneme kadar Ankara'da eşi ve evliliklerinden dünyaya gelen Besime Tomris isimli kızları ile yaşamlarını sürdürmüştür (1).

1940'lı yılların ortalarından itibaren Türkiye Cumhuriyeti bünyesinde iki tane tıp fakültesi bulunmaktaydı. Tüm ülkenin hekim ihtiyacı bu fakülteler sayesinde giderilmekteydi. Bu fakülteler; 31 Mayıs 1933'te İstanbul Darülfünunun İlgasına ve Maarif Vekâletince Yeni Bir Üniversite Kurulmasına dair kanun ile kurulan İstanbul Üniversitesi ile onun bünyesinde 4761 sayılı kanunun hükümlerine dayanarak oluşturulması planlanan ve gerçekleştirilen Ankara Üniversitesi Tıp Fakültesi'dir. Ayhan O. Çavdar, Cumhuriyet tarihimizin ilk tıp fakültesi olma şerefine nail olan Ankara Üniversitesi Tıp Fakültesi'ne, fakültenin kuruluşunun akabinde 1947 senesinde başlamış ve 1953'te mezun olmuştur (7-10).

Ayhan Çavdar, Tıp Fakültesi'nde öğrenci olduğu yıllarda kan hastalıklarına büyük ilgi duymuş, kendi ifadesiyle "kan hücrelerinin renkliliği ve kan hücrelerini mikroskop altında gözlemlemek" onu çok etkilemiştir. Bu dönemde Almanya Nazi yönetiminden kaçarak Türkiye'de görev yapan Prof. Dr. Eric Frank ve kendisinin notları, Ayhan Hoca için bulunmaz bir fırsat olmuş, bu alana olan ilgisi ve yönelimi iyice artmıştır. Bu tarihlerden sonra her bulduğu fırsatta trombositleri incelemek, kan hücrelerini gözlemlemek ve mikroskop önünde saatlerini geçirmek onun adeta tek uğraşı olmuştur (Fotoğraf 1) (3,11-13).

Mezuniyetini izleyen dönemde uzmanlık seçimi sırasında Ankara Üniversitesi'nin o dönemdeki çocuk hastalıkları klinik şefi Prof. Dr. Bahtiyar Demirağ, Ayhan Okçuoğlu Çavdar'ı çocuk asistanlığı için istemiştir. Bu değerli hocasının teklifiyle alana yönelen Ayhan Çavdar'ın çocuk asistanlığı sınavı, dönemin Çocuk Sağlığı ve Hastalıkları Doçenti olan İhsan Doğramacı tarafından yapılmıştır. Ayhan Okçuoğlu Çavdar, Doç. Dr. İhsan Doğramacı'nın sorduğu tüm soruları etraflıca cevaplayarak başarılı olmuş ve sonucun ardından teklifini yineleyen Prof. Dr. Bahtiyar Demirağ, Ayhan Çavdar'a birlikte çalışmayı istediğini belirtmiştir.

Ayhan Çavdar konu hakkında şöyle söylemektedir: "Dönem itibariyle Türkiye'de kadro almak kolay bir iş değildi. Başlarda kadrosuz olarak klinikte çalışmaya başladım. Ancak 5 ya da 6 ay sonra kadro alabildim" (3). Prof. Dr. Bahtiyar Demirağ'ın kliniğinde 1953'te başlayan asistanlık eğitimi büyük bir başarıyla 1956'da tamamlanmıştır. Asistanlık yılları süresince azmi ve

Fotoğraf 1: Ankara Üniversitesi Tıp Fakültesi, öğrencilik yılları/Aile arşivi

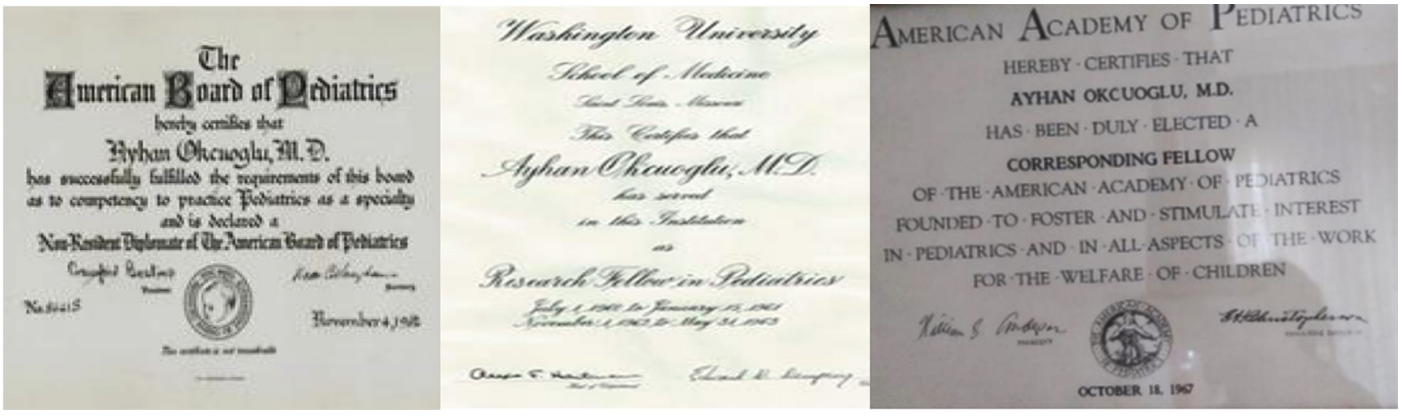
çalışkanlığıyla göz dolduran Ayhan Okçuoğlu Çavdar, asistanlık bitirme tezi konusu için araştırmaları sırasında "trombositler" üzerine çalışmak istediğine karar vermiştir. Ayhan Çavdar, dönem itibariyle Türkiye'de bu konuda hocalar dahi trombosit sayısını hesaplamakta ve saymakta zorlanmaktaydılar, bu alanda Türkiye için hematolojinin boşluk içinde olduğunu hissettiğini ve kan hücrelerine büyük ilgi duyduğunu belirterek, konuda uzmanlaşma isteğinde olduğunu ifade etmiştir (3).

İlerleyen yıllarda konunun Türkiye'de pek çalışılmadığını fark eden Ayhan Çavdar, bu konuda kusursuz eğitim alabilmek için yurt dışına çıkmayı planlamış ve Amerika'da St. Louis şehri Washington Üniversitesi'nde çalışan Alman kökenli Amerikalı Dr. Hartman'a mektup yazmıştır. Mektubunda, pediatrik hematoloji ve onkoloji üzerine çalışmak istediğini belirten Ayhan Çavdar, bir süre sonra Prof. Dr. Hartman'dan olumlu cevap almıştır. 1958 senesinde pediatrik hematoloji ve onkoloji yan dal eğitimi almak için Amerika Birleşik Devletleri'ne yola çıkan Dr. Ayhan Çavdar, Washington Üniversitesi'nde fellowlar için ayrılan klinik içerisindeki odalardan birine yerleşmiştir. Klinikte kalmayı tercih etmesinin sebepleri arasında, "geceleri dahi kliniği gezerek daha çok öğrenmek, hasta dosyalarını okuyarak hem İngilizcesini geliştirmek hem de dosyaları inceleyerek daha çok öğrenmek ve farklı bir ülkeye intibakını kolaylaştırmak" bulunmaktadır. İlerleyen günlerde gece mesailerinin fark edilmesi ve şüpheli bulunması üzerine Dr. Çavdar durumu klinik sorumlusu olan Dr. Hartman'a şöyle izah etmiştir: "Geceleri asla hastaların tedavilerine karışmıyor, bu durumun etik olmayacağından, sadece öğrenmek amacıyla incelemeler yapıyorum." Ayhan Çavdar'ın çalışkanlığı, azmi, dürüst ve etik çalışmaları hocası Prof. Dr. Hartman'dan da takdir görmüş ve gün geçtikçe kişilik yapısı daha da beğenilmiştir. Öyle ki, eğitiminin bitmesine yakın kendisine klinikte çalışma önerisinde bulunulmuştur. Ülkesine hizmet etme arzusu ağır basan bir Türkiye sevdalısı olan Ayhan Okçuoğlu Çavdar, Dr. Hartman'ın nazik teklifini geri çevirerek Türkiye'ye dönme hazırlıklarını eğitiminin bitimine doğru başlatmıştır (3,11-13). Prof. Dr. Hartman çok cazip bir öneri de bulunmuştur. Ayhan Hanım'a dönmeyi kesinlikle isteyip istemediğini tekrar sormuştur, ona kendi koltuğunu göstererek iki yıl sonra bu koltukta sen oturarak bu kliniği yönetebilirsin, demiştir. Çok mutlu olduğunu ve gururlandığını bildiren Ayhan O. Çavdar, "efendim, bu çok büyük bir teveccüh olur, ancak ben, Amerika'da kalırsam deryada bir damla olurum. Oysa Türkiye'ye dönersem henüz gelişmemiş bir dalı kurma ve hizmet etme imkânı bulurum. Onun için beni mazur görün, ben ülkeme döneceğim." şeklinde Dr. Hartman'ın bu nazik önerisini geri çevirmiştir (1-3).

Prof. Dr. Ayhan Çavdar, Amerikan Board of Pediatrics sınavını kazanan ilk Türk hekimlerinden biri olmasının yanı sıra, ardından Academy of Pediatrics'in ilk Türk hekimi ve son olarak da American Society of Pediatric Hematology and Oncology'nin asli üyelerinden biri olmuştur (Fotoğraf 2) (1-3).

1961 yılında hocası Prof.Dr. Bahtiyar Demirağ'ın yoğun ısrar ve talebiyle doçentliğe başvuran ve doçentlik unvanını alan Ayhan Çavdar, ABD'ye tekrar giderek Pediatrik Board sınavını kazanmış ve 1962 Kasımı'nda Board sertifikasını almıştır. Bu sertifika, Amerika Birleşik Devletleri'nde doktor olarak hasta muayene etme ve reçete yazma yetkisini sağlayan önemli bir belgedir. İlerleyen yıllarda Fullbright bursuyla tekrar Amerika'ya gitmiştir. İlk gittiği sırada tamamlayamadığı çalışmalarını ikinci ziyareti sırasında tamamlamış, bu süreç oldukça zorlu ancak başarılı bir şekilde sonuçlanmıştır. 1960'lı yıllarda Türkiye'de tıbbın diğer ülkelere kıyasla geri kaldığını ifade eden Ayhan Çavdar, Fullbright bursu ile Amerika'ya giderken çalışma konularını seçerken çok titiz davranmıştır. Özellikle Türkiye'nin ihtiyaç duyduğu alanlara ve ülkenin karşılaştığı sorunlara odaklanmıştır (1,3,11,14).

ABD'deki çalışma yılları sırasında tanıştığı, Washington Üniversitesi'nde Barness Hastanesi'nde bir süre laboratuvarında beraber çalıştığı Prof. Dr. Virginia Minnich'in Türkiye'ye Fulbright bursu ile gelmesi için büyük çaba sarf eden Ayhan Çavdar, Minnich ile birlikte ülkemizde modern hematoloji laboratuvarının kurulmasına büyük katkı sağlamıştır (1,3,11,14). Virginia Minnich, Türkiye'de bulunduğu süre boyunca Ayhan O. Çavdar ve ekibiyle birlikte ülkemize özgü önemli sorunlardan



Fotoğraf 2: Amerika'da eğitimi sırasında aldığı board sertifikası/Aile arşivinden/Aile röportajları

biri olan Türk çocuklarında kil (toprak) yeme anemisi üzerine çalışmıştır. Araştırmaları, bu aneminin oluşum mekanizmasını anlamaya yönelik yoğun bir şekilde sürdürülmüş ve bulguları, Ayhan O. Çavdar ve ekibini çinko ve diğer eser element eksiklikleri alanında yeni araştırmalara yönlendirmiştir (3,11,12).

Çalışma konuları içerisinde kansızlık tedavileri de büyük önem taşımaktadır. Ayhan Çavdar, kansızlık tedavisi gerektiren hasta gruplarına demir ve gelişme gerilikleri için ise çinko ile müdahale ettiklerini belirtmiştir. Bu tedavilerle, gelişme geriliği olan ergen hastalarda hormonal gelişmelere katkı sağlanabildiğini ekibiyle birlikte tespit ettiklerini ifade etmiştir. Çavdar, çalışma bulgularını uluslararası literatürle paylaşmış ve bulguları uluslararası katılımlı bilimsel kongrelerde sunarak büyük yankılar almıştır (1-3,11-15).

Prof. Dr. Ayhan Çavdar ve ekibinin çocuklarda kil ve toprak yeme hastalığı olarak bilinen Pika hastalığının çinko eksikliğine ve dolayısıyla kansızlığa yol açtığını gözlemlemesi, kendisi ve ekip arkadaşlarını "Eser Elementler" hakkında büyük çaplı araştırmalar yöneltmiş ve ortaya koyduğu çalışmalarıyla ülkemizin uluslararası arenada söz sahibi olmasını sağlamıştır. Eser element araştırmaları sonraki dönemlere de sarkacak öylesine yoğun bir çalışma sürecini içerir ki bu durum Ayhan Çavdar'ın zamanla yetişkin insanlarda çinko eksikliği konusuna da eğilmesini kolaylaştırmıştır.

Çalışma arkadaşlarıyla birlikte yaptığı çalışmalarla toprak yeme eğilimli insanlarda oluşan kansızlık vakalarında demir eksikliği yanında çinko eksikliğini de tespit etmişlerdir. Türkiye'de bu konuda çalışan ilk kişiler olan Ayhan O. Çavdar ve ekibinin çalışmalarına bakıldığında; Pika hastalığı olarak bilinen, gıda bakımından sorunlu ve beslenme değeri olmayan bu maddelerin ısrarla tüketilmesinin adı olarak bilinen hastalığa yöneliktir. Ayhan O. Çavdar, sadece bu konu üzerinde uzun süre çalışmalar yaptıklarını belirtmiş, çinko ölçümlerini ilk olarak başlatan fakültenin ise Ankara Üniversitesi Tıp Fakültesi olduğunu pek çok gazete ve programlara verdiği konuşmasında vurgulamıştır. Önceleri uzun süreler sadece toprak ve kil yiyen çocuk hastaları inceleyen ekip bu eksikliği ilerleyen yıllarda annelerde de ölçmeye başlamışlar ve oldukça önemli veriler edinmişlerdir (1,3,11-13). Bu eksikliğin annelerde düşük gebeliklere sebep olduğunu saptayan Dr. Çavdar ve ekibi Türk bilim dünyası için oldukça önemli bu bulguyu da dünya literatürüyle paylaşmışlardır.

Ayhan Çavdar, konuyla ilgili söylemlerinde bu eksikliğin kansızlık da yaptığını, ayrıca demir eksikliğine de yol açmakta olduğunu belirtmiştir. Hasta tedavileri sırasında hasta çocuklara ilk olarak demir takviye edilmiş, demir beklenen sonucu yaratmayıp ne beyin ne de hormon gelişimine yol açmayınca, kansızlık probleminin çözülmesinin ardından çocuklara çinko verilmesi ile tedaviye devam edilmiş, bu uygulananların çocuklarda hızlı bir şekilde boy uzamasına sebebiyet verdiği, hormonal gelişmeler sağladığı gözlenmiştir. Böylece uygulanan bu tedavinin devam ettirilmesi sağlanmıştır (1,3,11-13).

Çocuklara demir verilmesinin katkı sağlamamasıyla Dr. Çavdar ve ekibi ülkemizde yaptığı gözlemlerde hem çocuk hem de gebe kadınlarda daha çok besinsel gelişen çinko eksikliğini ortaya koymayı başarmış, çok sayıda hastalığa da (orak hücre kansızlığı, Hodgkin hastalığı ve diğer kan hastalıkları, Thalassemia Major) eşlik eden çinko eksikliği bulgusunu böylelikle tanımlayabilmişlerdir (1,3,11-13).

Çalışmalarının çoğunu bu konuya yönelten Ayhan O. Çavdar, konunun önemli kaynakları içerisinde yer alacak "Zinc Deficiency in Human Subjects" adlı uluslararası nitelikli kitabın da editörleri arasında yer almayı başarmıştır. 1983 yılında, Amerika'da basılan ve literatüre eklenen "Zinc Deficiency in Human Subjects" isimli kitap Çavdar'ın en önemli çalışmaları içerisindedir (1,3,11-13).

Çocukluk çağı lenfomaları da Ayhan Çavdar'ın üzerine yoğunlaştığı çalışmalar içerisindedir, özellikle Hodgkin hastalığı ve Burkitt lenfoması. Bu hastalarda yaptığı pek çok ölçümde MC (Mixed Cellular) histopatoloji tipinin yüksekliğini ve hastaların yüksek bir miktarının erkeklerde yaygınlığını ve alt sosyo-ekonomik gruba ait olduğunu ortaya koymuştur. Yine önemli bir yenilik olarak löseminin bir türü olan, akut myeloid lösemilerin ülkemiz hastalarında gözde tümör formları oluşturduğunu ve bunun gelişmiş ülkelerde nadir görülen bir durum olduğunu ekibiyle yapmış olduğu yoğun çalışmalar sonrasında tespit etmişlerdir (Orbital Granülositik Sarkoma-OGS) (1,3,11-13).

Bu durumun özellikle az gelişmiş ülkelerde çokluğuna dikkat çeken Ayhan Çavdar ve çalışma arkadaşlarının Hodgkin hastası çocukların çinko düzeylerinin düşüklüğünü saptamaları da ayrıca tüm dünyada büyük ilgi toplamıştır. İlerleyen yıllarda yapılan bu çalışmalar dünyanın merakı ve ilgisini iyice bu konuya kanalize etmesine sebep olmuş, Prof. Dr. Ayhan Çavdar bu alanda çalışanlar arasında dünya çapında "Bayan Çinko" olarak anılır hale gelmiştir (1,3,11-13).

Çavdar durumu şöyle açıklamaktadır: "Türk çocuklarımızda akut lösemilerden sonra en sık yakaladığımız malign lenfomalardan Hodgkin hastalığı hakkında uzun süre çalıştım. Oldukça ilginçtir ki, 0-6 yaş arasında bile Hodgkin hastalığına rastladık. Konuyu Paris'te düzenlenen uluslararası bir kongrede tanıttım. Çalışmalar sırasında ilgimizi çeken en önemli şey Hodgkin'li çocukların ailelerinin sosyo-ekonomik yapısının genellikle alt düzeyde olduğuydu. Ülkemizde bu yaşlardaki çocuklarda bu hastalığın küçümsenmeyecek sayıda olduğunu gördük, tüm kongrelerde bulgularımızı sözel olarak sunduk. Bu ailelerin çocuklarının sadece enfeksiyona yatkınlıkları değil, beslenme bozukluğu belirtilerine de sahip olduklarını farkettik. İnsanlarda çinko eksikliğini bulan Prof. Dr. Prasad'dan sonra Hodgkin hastalığında çinko eksikliğine vurgu yaptık. Bulgularımız sonrasında kendisiyle mektuplaştık. Bulduğumuz

bu sonuçlara büyük ilgi göstererek Türkiye'de uluslararası Çinko Kongresi düzenlemeyi planladık ve 1982'de Ankara'da düzenlenen kongrenin kitabı ise ABD'de yayınlandı (benim adımı da içeriyordu). Düzenlediğimiz bu çok önemli kongreye Avrupa ve ABD'den birçok konu hakkında kafa yoran bilim adamı katıldı." (1-3,11,13).

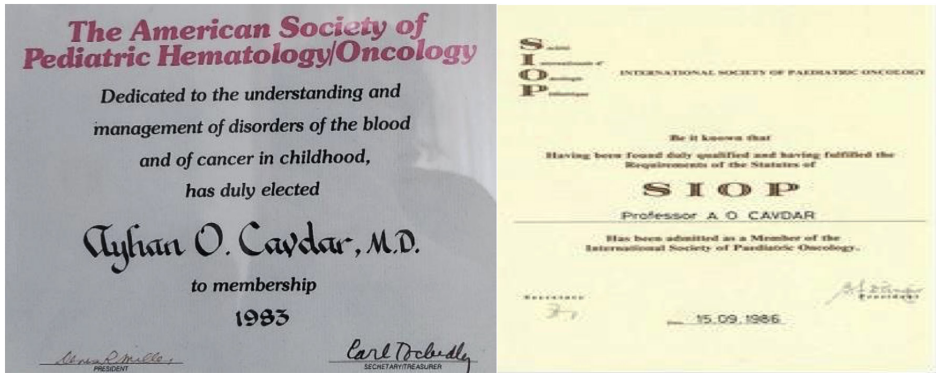
Bilime ve ülkemiz sorunlarına yönelik çalışmalara önem veren Prof. Dr. Ayhan O. Çavdar doçent olduktan sonra o tarihlerde Numune Hastanesi'nde hizmet veren Çocuk Hastalıkları Kliniği içinde, Pediatrik Hematoloji-Onkoloji Bölümü'nü kurmuştur. Süreci şöyle anlatmıştır: "..izlediğimiz karnı şiş, rengi solgun ve kansızlık olan bir çocuk hasta vardı. Çocuğun teşhisi tüberküloz olarak konulmuştu. Hastaya kemik iliği aspirasyonunu bizzat yaptım ve çocukta akut lösemi olduğunu saptadım. Preparatı hocaya gösterdim ve durumu ayrıntısıyla anlattım. Sonrasında da lösemili çocuklar için kabilse ayrı bir oda ve birkaç yatak istedim." (1-3,11). 1967 yılında profesörlüğünü alan Çavdar, yine 1967'de Türk Hematoloji Derneği'nin kuruluşuna ve derneğin tüzüğünün hazırlanmasına kadar pek çok aşamasına öncülük edenler arasındadır (1-3,14). International Pediatric Oncology Society Türkiye'den seçilen ilk üyelerinden birisi yine Prof. Dr. Ayhan O. Çavdar'dır (11).

Profesör olduktan sonra benzer konularda çalışmalarını sürdüren Ayhan Çavdar, çocuklarda "akut lösemileri"n en sık gördükleri hastalıkların başında geldiğini ortaya koymuştur. Konuyla ilgili Ayhan O. Çavdar, gözünde tümör çıkan bir hasta için bir hekim arkadaşının kendisini aradığını, kan sayımı yapmasını istediğini, sonuca göre hastaya enükleasyon yapmayı planladıklarını anlatmıştır. Periferik kanda monoblastlar gördüklerini, kemik iliği ölçümlerinin ise monobastlar ile dolu olduğunu fark ettiklerini belirten Prof. Dr. Ayhan Çavdar, hemen hastaya kemoterapi tedavisine başladıklarını, bu olaydan sonra kan ve kemik iliği muayenesine daha çok önem verdiklerini, fırlamış gözleri kemoterapi ile remisyondan önce düzelttiklerini anlatmıştır. Olayı yurt dışı literatürüyle paylaştığında büyük yankı aldığını belirten Ayhan O. Çavdar konuyla ilgili şunları söylemiştir: "Amerika bilimsel bulgularda kolay ikna olmazdı, bu yüzden bu hastalara ait kemik iliği preparatlarıyla Amerika'ya gittik, çok şaşırdılar ancak böylece ikna oldular," diyerek eklemiştir. "...böylece akut melablastik löseminin gözde tümör yaptığı anlaşıldı. Yayınımız çok beğenildi, bu konuyla ilgili çok atıf aldık, ardından Hindistan'dan benzer yayınlar gelmeye başlamıştı. Bizde akut melablastik lösemi gözde tümör yaparken Amerika'da yapmıyor, çok şaşırtıcı sonuçlardı bunlar ve çok ilgi uyandırdı. Ankara Üniversitesinde yaptığım virüs incelemelerinde yine düşük sosyo-ekonomik düzeydeki ailelerin çocuklarında en sık görülen tümörün malin lenfoma olduğunu gördük" (1,3,12).

Prof. Dr. Ayhan Çavdar, çocuklarda kanser ve kan hastalıkları üzerine yapılan araştırmalara önemli katkılarda bulunmuştur. 1975 yılında kurulan TÜBİTAK'a bağlı Pediatrik Onkoloji ve Hematoloji Araştırma Ünitesi ve ayrıca 1975-1981 yılları arasında TÜBİTAK desteğiyle, "Kanser ve Kan Hastalıkları Araştırma Ünitesi" Prof. Dr. Ayhan Çavdar tarafından kurulmuştur. Mediterrenian Blood Club-MBC'nin 1975 yılında kuruluşunda yer alan Prof. Dr. Ayhan Çavdar, 1993-1995 yılları arasında bu kuruluşun başkanlığını üstlenmiştir.

Çavdar, çocuklarda Pika, Thalassemia Major ve Hodgkin hastalığı üzerine yaptığı araştırmalarla çinko eksikliğini göstermesi çalışmalarıyla Türkiye'de Pika (Toprak Yeme) probleminin araştırılması projesini ilk kez TÜBİTAK desteğiyle hazırlamıştır. 1982-1984 yılları arasında Prof. Dr. Ayhan Çavdar, TÜBİTAK Araştırma Grubu (TAG) üyeliğine seçilmiş ve 1982 yılında Prof. Dr. A. Prasad'ın işbirliği ile Ankara'da İlk Uluslararası Çinko Sempozyumu düzenlenmiştir. 1983 yılında American Society of Pediatric Hematology and Oncology'ye Türkiye'den Prof. Dr. Ayhan Okçuoğlu Çavdar ilk üye olarak seçilmiş, ayrıca Türkiye'den davet edilen ilk kişi olarak International Society of Pediatric Oncology'nin (*SIOP-Societe International d'Oncologie Pédiatrique*) üyeliğine 1986 yılında seçilmiştir (Fotoğraf 3) (1,3,11).

Prof. Dr. Ayhan Çavdar, Zinc Deficiency in Human Subjects adlı kitabın editörlerinden biriydi ve TÜBİTAK'ın İngilizce yayınladığı Trace Elements in Humans ve TÜBA tarafından yayınlanan Kanser ve Etik kitaplarının da editörlüğünü yapmıştır. Ayrıca, 2006'da



Fotoğraf 3: SIOP ve *American Society of Pediatric Hematology/Oncology* kuruluşları üyelik belgeleri/Aile arşivinden/Aile röportajları

SIOP: International Society of Pediatric Oncology-*Societe International d'Oncologie Pédiatrique*

düzenlenen Uluslararası Selenyum Sempozyumunda İngilizce yayınlanan kitabı Dr. Filiz Hıncal ile birlikte hazırlamıştır. Prof. Dr. Ayhan Çavdar'ın pediatrik hematoloji ve onkoloji hakkında 12 monografisi bulunmaktadır. Pek çok kongre ve sempozyumda başkan ve düzenleyici olarak görev almış ve çok sayıda davetli konferans vermiştir. Mart 2024 itibariyle erişilebilen 278 adet İngilizce yayını bulunmaktadır ve toplamda 475 yayına sahiptir. Tüm yayınlarına 2000 civarında atıf almıştır ve Science Citation Index tarafından taranan dergilerde yayınlanan yaklaşık 200 makalesi bulunmaktadır. Özellikle "Geophagia in Turkey: iron and zinc deficiency, iron and zinc absorption studies and response to treatment with zinc in geophagia cases." başlıklı makalesi, 2024 Mart ayı verilerine göre 849 atıf almıştır (12,13).

Efsane Hoca Ayhan Okçuoğlu Çavdar'ın Kişisel Özellikleri

Ayhan Okçuoğlu Çavdar, öğrencilerine olan saygı ve sevgisiyle bilinen, disiplinli, özverili ve gelişime açık bir öğretim elemanıydı. Hem yaptığı çalışmaların incelenmesi hem de çevresindekilerin beyanları, onun öğrencileri üzerinde önemli bir etki yarattığını göstermektedir. Öğrencileri, onun çalışma ortamında her zaman bir lokomotif gibi davrandığını ve öğrencilerine örnek olduğunu ifade etmektedirler. Öğrencilerinden Prof. Dr. Sevgi Gözdaşoğlu ile yapılan telefon görüşmesinde, hocasıyla ilgili şunları söylemiştir: "Ayhan Çavdar, hayatı, hayatı algılayışı, aklı, fikri, araştırmayı sevmesi, azmi ve araştırma yöntemleri ile hep örnekti. Öğrendiklerini herkesle sakınmadan paylaşırdı. Fark ettiği veya bulduğu bilgiyi asla saklamazdı. Çok çalışkandı ve aslında saklamayarak ne kadar akıllı olduğunu da görürdük. Her dakika değişen bilgiyi saklasa ne olacaktı, bir süre sonra değişecek bilgiyi saklamaktansa paylaşıp onları geliştirmeyi severdi. Bir araştırma planladığında veya bir bulguyla karşılaştığında çok heyecanlanırdı. O konuyu derinlemesine araştırır, laboratuvarına kendi girer, ölçümlerini yapardı. Sabahları gelir gelmez çantasını bırakır, günaydın der, önlüğünü giyer ve hemen okuduğu ve bulduğu yenilikleri anlatırdı. Bizde doçentlik veya profesörlük tezleri hep Ayhan hocanın önerileri olurdu".

Bu tanıklıklar, Ayhan Okçuoğlu Çavdar'ın sadece bilimsel alanda değil, öğrencileriyle kurduğu örnek ilişkilerle de hatırlanmasının önemini vurgulamaktadır (15).

Prof. Dr. Mustafa Çetiner, Ayhan Çavdar'dan bir öğretmen olarak bahsetmekte ve onunla ilgili anılarını şöyle ifade etmektedir:

"...Ayhan Çavdar Okçuoğlu öğretmen ile ilk karşılaşmam 1986 yılındaydı. Ankara Tıp Fakültesinde öğrenciydim ve pediatri stajındaydık. Ayhan öğretmenin dersinin olduğu gün bölüm çalışanlarında, asistanlarda büyük bir telaş olduğunu hatırlıyorum. O zamanlar neden bu kadar büyük bir heyecan yaşandığını tam anlayamamış ve hatta anlam da verememiştim. Ders saati amfideki yerlerimizi aldık, dersin ismi "Çinko" idi.." (16).

Prof. Dr. Ayhan Çavdar'ın yardımseverliği yanında olay ve kişilere duyarlı yapısı hekimlik ahlakı içerisinde önemli değerleri içerisindedir. Hastalarını her zaman gözetir ve durumlarını yakından takip ederdi. Ayhan Çavdar, hastalıklarının tanısı ve tedavisi sırasında hastalarıyla ilişkilerini çok yakından devam ettirdiğini kendisi de pek çok demecinde belirtmiştir. Adaletli bir yapısı olan ve haksızlıklar karşısında durmayı her zaman başaran Ayhan Okçuoğlu Çavdar'ın kişisel mevzuları ile iş yaşamını asla birbirine karıştırmadığı, karşısındaki insan ile ilişkilerini profesyonellik ilişkileri doğrultusunda yürüttüğü çalışma arkadaşlarının dile getirdiği en önemli konulardandır. Uzun yıllar birlikte çalıştığı Sevgi Gözdaşoğlu'nun beyanları Ayhan O. Çavdar'ın insanlarla olan ilişkisinin profesyonel ve eşitlik ilkeleri doğrultusunda olduğunu gözler önüne sermektedir. Sevgi Gözdaşoğlu, "diyelim ki hocanın anlaşamadığı bir insan var ve kürsü de kişiye haksızlık edildiğini fark ediyor, hemen müdahale ederek durumu çözmeye çalışırdı. Bu da kendisini diğer pek çok insandan ayıran en önemli ve güzel özelliklerinden biriydi." diye durumu anlatmaktadır (15).

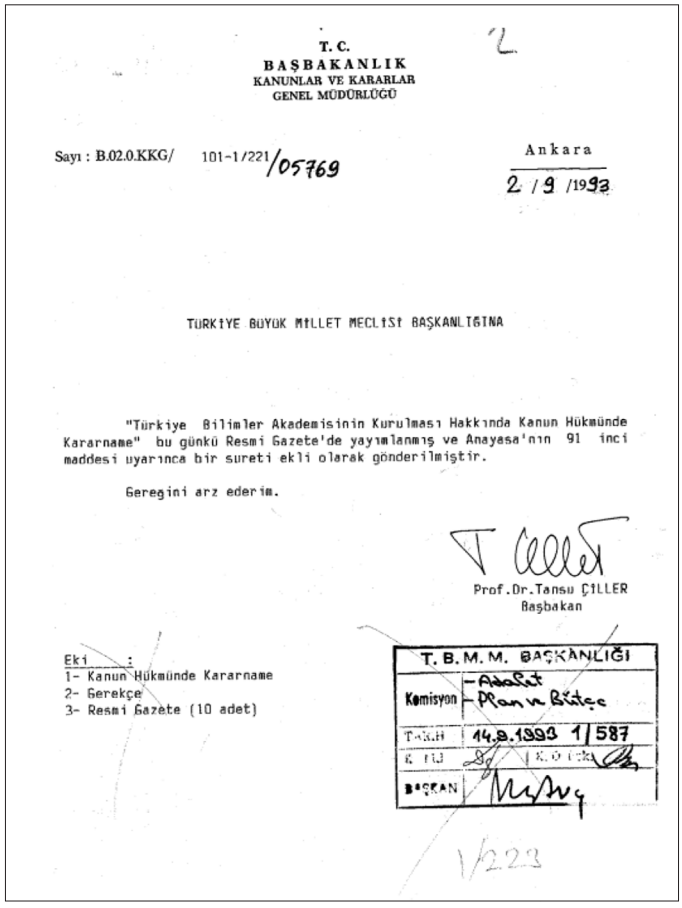
Türkiye Bilimler Akademisi'nin Kuruluşu-TÜBA ve İlk Kadın Başkan Prof. Dr. Ayhan Çavdar

Platon'un kurduğu akademi, dünyada ilk bilim akademisi olarak kabul edilir. Türkiye Cumhuriyeti'nde, bilimin tüm alanlarına katkı sağlayacak bir bilimler akademisi kurma fikri 1960'lı yıllarda ortaya atılmış olsa da, TÜBA'nın tüm bilim alanlarına özgü, özerk ve ulusal bir yapılanma ile 1993'te kuruluşunu tamamlamıştır (17).

TÜBA, bilimsel alandaki araştırmaları desteklemek, genç ve bilimle ilgilenenleri bilimsel araştırmalara yönlendirmek, bu alanda çalışmalar yapmak amacıyla, Başbakan'a bağlı, tüzel kişiliğe sahip, bilimsel, idari ve mali özerkliği bulunan TÜBA'nın kurulmasını öngörmektedir. 27/1 dönem ve yasama yılında 1/177 esas numara ve 497 Kanun Hükmünde Kararname içeriğiyle 02/09/1993 tarihinde kuruluş aşamasının tamamlanma adımları atılmıştır (Fotoğraf 4) (17,18).

TÜBA'nın organlarının, Aralık 1995 tarihli TÜBA bülteninin 1. sayısında, Kanun Hükmünde Kararname'nin 6. maddesinde belirtildiği şekilde düzenlendiği görülmektedir. Bu organlar şunlardır: Akademi Genel Kurulu (Akademi Üyelerinden oluşur), Akademi Konseyi (Akademi Kurulunca 4 yıl için seçilen 10 asil üye ile başkandan oluşur) ve Akademi Başkanı. Akademi, Asli Üye, Asosye Üye ve Şeref Üyesi olmak üzere üç tür üyelikten oluşmaktadır (19).

TÜBA'nın kuruluş döneminde ülkenin başbakanı Süleyman Demirel, başbakan yardımcısı ise Prof. Dr. Erdal İnönü'dür. TÜBA'nın ilk seçimlerinde Prof. Dr. Ayhan O. Çavdar da dahil olmak üzere 10 kurucu üyenin seçilmesinin ardından, bu 10



T. C.
BAŞBAKANLIK
KANUNLAR VE KARARLAR
GENEL MÜDÜRLÜĞÜ

Sayı : B.02.0.KKG/ 101-1/221/05769

Ankara
2 / 9 /1993

TÜRKİYE BÜYÜK MİLLET MECLİSİ BAŞKANLIĞINA

"Türkiye Bilimler Akademisinin Kurulması Hakkında Kanun Hükmünde Kararname" bu günkü Resmi Gazete'de yayımlanmış ve Anayasa'nın 91 inci maddesi uyarınca bir sureti ekli olarak gönderilmiştir.

Gereğini arz ederim.

Prof.Dr.Tansu ÇİLLER
Başbakan

Eki :
1- Kanun Hükmünde Kararname
2- Gerekçe
3- Resmi Gazete (10 adet)

T. B. M. M. BAŞKANLIĞI
Komisyon - Adalet - Plan ve Bütçe
T.B.M.M 14.9.1993 1/587
BAŞKAN

Fotoğraf 4: 27/1 dönem ve yasama yılı 1/177 esas numara ve 497 KHK, TBMM arşivi

TBMM: Türkiye Büyük Millet Meclisi

üyenin gizli oyuyla diğer 10 üyenin de seçildiği görülmektedir. Böylece 20 kişiden oluşan üyelerin katılımıyla ilk genel kurul oluşturulmuştur. Prof. Dr. Ayhan Çavdar, 10 kurucu üye arasında yer alması ve çoğunluğu erkeklerden oluşan üyelerin gizli oylarıyla Bilimler Akademisi başkanlığına getirilmiştir. Kendisinin seçilmesi sadece bilimsel yetkinliğiyle değil, kısmen kişilik özellikleriyle de açıklanabilir. Seçimler sırasında, "ikinci on üyeyi seçerken yapılan hararetli tartışmaların üyelerin kendisi hakkında fikir edinmelerine olanak sağladığını" belirten Prof. Dr. Ayhan O. Çavdar, yapılan tartışmaların onun lehine oy kullanılmasını ve başkan olarak seçilmesini kolaylaştırdığını ifade etmiştir (Fotoğraf 5) (1,17-20).

TÜBA, kurulduğu dönemde faaliyetlerine hızla başlamış ve öncelikle üye seçimlerini gerçekleştirmek, bu seçimleri bilimsel liyakat esaslarına göre yapmak gibi konulara odaklanmıştır. Prof. Dr. Ayhan O. Çavdar'ın başkanlığı aldığı günden görevden ayrıldığı tarihe kadar üye sayısı 108'e kadar ulaşmıştır. TÜBA Şeref Üyeleri de dahil edildiğinde toplam üye sayısı 30 Şeref Üyesi, 73 Asli Üye, 9 Asosiye Üye ile 112'ye yükselmiştir. Bu durum, Bilimler Akademisi'nin itibarını artırmış ve ülkemiz bilim dünyası için bir gurur kaynağı olmuştur. TÜBA'nın ilk seçiminde, Cumhuriyet Türkiyesi'nin bir sonucu olarak kadın bir başkanın seçilmesi bir ilktir ve bu olay Avrupa'nın ilk kadın başkanları içerisinde olmasıyla daha da vurgulanmıştır. Ayhan Çavdar ile Yücel Kanpolat'ın gerçekleştirdiği söyleşide, üyelerin %16'sının kadın üyelerden oluştuğu belirtilmiştir. Bu oranın dünya genelindeki bilim akademilerindeki oran olan %3'ten oldukça yüksek olduğu görülmüştür. Ayhan Çavdar, bu durumu önemli bir husus olarak vurgulayarak, Türkiye'deki bilim akademisi başkanının bir kadın olması ve üyelerin %16'sının kadın üyelerden oluşmasıyla ilgili dünya rekorunun Türkiye'de olduğunu belirtmiştir. Bu durum, Avrupa'dan gelen tebrik mesajlarıyla daha da gurur verici bir hal almıştır (3).

Ayhan O. Çavdar, 1993'te ilk kez ve 1997'de ikinci kez TÜBA Başkanlığı'na seçilmiş ve bu süre zarfında birçok toplantı düzenlemiştir. Ayrıca, TÜBA içinde önemli bir oluşum olan Kanser Çalışma Grubu'nu kurarak başkanlığını üstlenmiştir. Çalışmaları sonucunda Prof. Dr. Çavdar, İstanbul'un Kadın Sorunları Araştırma ve Uygulama Merkezi'nin Aydınlanmanın Kadınları Ödülü'ne layık görülmüştür. Başkan olarak görev yaptığı dönemde, 20 kitap, 15 TÜBA Bülteni ve "Türkiye Cumhuriyeti'nin 75. Yılında Bilim" bilanço çalışmaları sonrasında ulusal ve uluslararası toplantılar düzenleyerek akademi bünyesinde kapsamlı ve içerik açısından zengin 5 kitabın yayınlanmasına öncülük etmiştir (1,2,12,13,17-19).

Diğer Dernek Çalışmaları ve Son Yılları

Prof. Dr. Ayhan O. Çavdar ve Avukat Arif Çavdar sadece kurucu üyelik değil, 31 Aralık 1989 tarihinde ADD kurucu genel başkanı Prof. Dr. Muammer Aksoy'un şehit edilmesinden sonra Dördüncü Genel Başkanlık görevini de üstlenmiş ve sürdürmüştür. Derneğin bütçesinin o dönemde son derece kısıtlı olması nedeniyle, ADD'nin bütün çalışmaları, Sn. Arif Çavdar'ın kendi sınırlı olanakları ile özel bürolarından birisini de dernek çalışmalarına tahsis etmesiyle sürdürülebilmiştir. ADD'nin Türkiye'nin çeşitli illerinde açtığı şube açılışlarına Prof. Dr. Ahmet Taner Kışlalı ile birlikte çok yönlü destek veren Sn. Arif Çavdar olmuştur. 1995 yılında aile fertleriyle birlikte saygın ve aydın Türk düşünürlerinin de katılımıyla ATASEV-Atatürk Sanat, Sağlık, Eğitim Vakfı'nı kurmuştur (20).

1967 yılında 5253 sayılı Dernekler Kanunu uyarınca kurulan İstanbul merkezli Türk Hematoloji Derneğinin 27 Nisan 2013 tarihli tüzüğü gözden geçirildiğinde Ayhan Okçuoğlu Çavdar'ın kurucu üyeler içinde yer aldığı ve derneğin 2. başkanı olduğu görülmektedir.

Ülkemizin tıp alanındaki en köklü bilimsel derneklerinden biri olan Türk Hematoloji Derneği (THD) 1967 yılında İstanbul'da, Prof. Dr. Orhan Ulutin'in (1924-) öncü girişimiyle, diğer hocalarımız Ord. Prof. Dr. Sedat Tavat (1892-1973), Ord. Prof. Dr.

Prof. Dr. Ayhan Çavdar

1953 yılında Ankara Üniversitesi Tıp Fakültesi'nden mezun oldu.
Çeşitli Avrupa ve Amerika kliniklerindeki çalışmalarından sonra 1987 yılından bu yana Ankara Üniversitesi Pediatrik Hematoloji- Onkoloji Araştırma ve Uygulama Merkezi Başkanlığını yürütüyor.
1976 yılında aldığı TÜBİTAK Bilim Ödülü'nü sıra birçok ödülü bulunan Prof. Dr. Ayhan Çavdar yerli ve yabancı çeşitli bilim akademilerinin üyesi olup Çocuk hastalıkları Araştırma Vakfı'nın da başkanıdır.

Prof. Dr. Burak Erman

1967 yılında Robert Kolej'den İnşaat mühendisi olarak mezun olmuştur. İstanbul Teknik Üniversitesi'nde doçent ve profesör olmuştur. Halen Boğaziçi Üniversitesi'nde görev yapmaktadır.
1983 yılı TÜBİTAK Teşvik ve 1991 yılı TÜBİTAK Bilim Ödülü sahibi olan Prof. Dr. Burak Erman Bilim birçok bilim dergisinde yayın kurulu üyesidir.

Prof. Dr. Metin Heper

1963 yılında İstanbul Üniversitesi'nden mezun oldu. Boğaziçi Üniversitesi'nde doçent ve profesör olan Prof. Dr. Metin Heper halen Bilkent Üniversitesi Siyasal Bilgiler Fakültesi Kamu Yönetimi Bölümü'nde görev yapıyor.
Amerikan Araştırma Enstitüsü Yürütme Komitesi üyeliğini yapan Heper, çeşitli bilim akademilerinde de üyedir.

Prof. Dr. Yavuz Nutku

1965 yılında California Üniversitesi'nden mezun oldu. Chicago Üniversitesi Fizik dalında doktora çalışmasını tamamlayan Nutku, ODTÜ'de doçent, Boğaziçi Üniversitesi'nde Prof. oldu.
Çeşitli yabancı üniversitelerde çalışmalar yapan Nutku halen Bilkent Üniversitesi Matematik Bölümü'nde görev yapıyor.1975 yılı TÜBİTAK Teşvik ve 1989 yılı TÜBİTAK Bilim Ödülü sahibi ve çeşitli Türk ve yabancı fizik ve matematik dernekleri'nin üyesi.

Prof. Dr. Murat R. Sertel

1963 yılında Robert Kolej'den mezun oldu. 1974 yılında Wissenschaftszentrum Berlin'de profesörlüğe yükseldi. Halen Boğaziçi Üniversitesi'nde görev yapıyor.
Journal of Economic Desing adlı bilimsel dergi'nin başeditörlüğünü yapmaktadır. Ödüllü aşkın makalesi ve bir kitabı bulunmaktadır.

Prof. Dr. Mithat İdemen

1958 yılında İstanbul Teknik Üniversitesi Elektrik Fakültesi'nden mezun olmuştur. Paris Fen Fakültesi Elektronik Enstitüsü'nde 1975 yılında profesör olan Prof. İdemen halen TÜBİTAK Marmara Araştırma Merkezi Matematik Bölüm Başkanlığı görevini sürdürmektedir.
1983 yılında TÜBİTAK Bilim Ödülü'nü kazanan Prof. Dr. Mithat İdemen çeşitli yabancı matematik ve fizik dergilerinde hakemlik görevini sürdürmektedir.

Prof. Dr. M. Gündüz İkeda

1948 yılında Osaka Üniversitesi Matematik Bölümü'nden mezun olmuştur. Türkiye, Japonya, Avrupa ve Amerika'daki çeşitli üniversitelerde çalışmalarını sürdüren Prof. Dr. Gündüz İkeda 1992 yılında ODTÜ'den emekliye ayrılmıştır. 1979 yılı TÜBİTAK Bilim Ödülü sahibidir.

Prof. Dr. Ali Cumhur Ertekin

1961 yılında Ege Üniversitesi Tıp fakültesi'nden mezun olmuştur.Çeşitli Avrupa ülkelerinde değişik üniversitelerde çalışmalarını sürdürmüş, halen Ege Üniversitesi Tıp Fakültesi'nde öğretim görevlisi olarak çalışmaktadır.
Birçok bilimsel kuruluşun üyesi olan Prof. Dr. Ali Cumhur Ertekin 1991 yılı TÜBİTAK Bilim Ödülü sahibidir.

Prof. Dr. Şefik Süzer

1970 yılında Orta Doğu Teknik Üniversitesi Kimya Bölümü'nden muzun olmuştur. Daha sonra çalışmalarını Amerika, Avustralya, Almanya sürdürmüş 1992 yılında ODTÜ'de profesör olmuştur. Halen çalışmalarını Bilkent Üniversitesi Fen Fakültesi Kimya Bölüm Başkanı olarak sürdürmektedir. Çeşitli burslar kazanan Prof. Dr. Şefik Süzer, 1990 yılı TÜBİTAK Bilim Ödülü sahibidir. Çeşitli bilimsel dergilerin yayın kurulu üyeliği ve Türkiye temsilcilikleri yapmıştır. Türk Kimya Derneği ve Amerikan Kimya Derneği üyesidir.

Prof. Dr. Kazım Türker

1952 yılında İstanbul Üniversitesi Tıp Fakültesi'nden mezun olmuştur. Amerika'da çalışmalarını sürdüren Prof. Dr. Kazım Türker, 1972 yılından beri Ankara Üniversitesi Tıp Fakültesi Farmakoloji Anabilim dalı Başkanlığı görevini sürdürmektedir.
Cumhuriyetin 50. Yılı TÜBİTAK Tıp Bilim Ödülü, 1974 yılı TÜBİTAK Bilim Ödülü sahibi olan Prof. Türker, European Journal of Pharmacology Editörler Kurulu üyesi olup sürekli danışmanıdır. Ayrıca, Türk Hemotoloji ve Türk Fizyoloji Derneği'nin üyesi Türk Farmokoloji Derneği'nin başkanıdır.

Prof. Dr. Tosun Terzioğlu

1965 yılında Newcastle Upon Tyne Üniversitesi, Matematik Bölümü'nden mezun olmuştur.Yurtdışında çalıştığı periyotların dışında 1968'den beri sırasıyla ODTÜ Matematik Bölüm Başkanlığı, ODTÜ Fen Ve Edebiyat Fakültesi Dekanlığı, Senato üyeliği, Temel Bilimler Araştırma Grubu üyeliği, ODTÜ Öğretim Üyeleri Yönetim kurulu Başkanlığı görevini sürdürmüstür. halen Türk Matematik Derneği'nde yönetim kurulu başkanlığını sürdürmektedir. NATO Doktora Bursu'na hak kazanan Prof. Dr. Tosun Terzioğlu 1971 Balkan Matematikçiler Birliği Genç Araştırıcı Ödülü, 1974 TÜBİTAK Teşvik Ödülü, 1986 yılında TÜBİTAK Bilim Ödülü'nü kazanmıştır.
Çeşitli bilim yayınlarının editörlüğünü de yapan Tosun Terzioğlu'nun 45 bilimsel yayını bulunuyor ve TÜBİTAK Başkanlığını sürdürüyor.

Bilim adamlığı özendirilecek

Akademi Başkanı Ayhan Çavdar'la söyleşi. "Yeni üyeler titizlikle seçilecek"

Türkiye Bilimler Akademisi Başkanlığına seçilen Prof. Dr. Ayhan Çavdar, 1958-1969 yılları arasında Amerika'nın çeşitli üniversite hastahanelerinde, enstitülerinde, çocuk kanser merkezlerinde ve Montreal'da Gill Üniversitesi'nde çalışmalarda bulundu. Ülkemizde de TÜBİTAK bünyesinde çeşitli üniteler kurdu ve yönetti. 1987 yılından bu yana Ankara Üniversitesi Pediatrik Hematoloji - Onkoloji Araştırma ve Uygulama Merkezi Başkanlığı yapmaktadır.
Ayhan Çavdar Türkiye Bilimler Akademisi Başkanlığına seçildikten hemen sonra sorularımızı yanıtladı.

Soru- TÜBA kısa vadede, hemen önümüzdeki dönemde neler yapmayı planlıyor?
Çavdar- TÜBA kısa vadede, örgütlenme, bilgi derleme, değerlendirme, bilim çevreleri ve devlet hükümet yetkilileriyle iletişim kurmak gibi hazırlık ve planlama çalışmaları yapma konumundadır. Bu bağlamda, yasaların öngördüğü amaçların gerçekleştirilmesi için yapılması gereken düzenlemeler yönünden tüzük, yönetmelik ve gerekirse yönergeler hazırlanması kaçınılmazdır.
Öte yandan dünyadaki bilim akademilerini incelemek ve onlarla iletişim kurmak, TÜBA'nın kısa vadeli program çalışmaları arasında sayılabilir.

Soru- Akademi'nin ülkemiz bilim hayatına uzun vadeli katkıları neler olacak?
Çavdar- Türkiye'de tüm bilim alanlarında araştırmaları, bilimsel kişiliği ve araştırmacılığı özendirmek; bu alanlarda emeği geçenleri onurlandırmak; gençleri bilim ve araştırma alanlarında daha fazla yönlendirmek; Türkiye'deki bilim adamlarının toplumsal statülerini ve yaşam düzeylerini yükseltmek ve korumak; toplumda standartların uluslararası düzeye çıkartılmasına yardım etmek; bilim adamlığını özendirmek için "ödüller" vermek.

Soru- Ülkemizde bilim ve araştırmanın önündeki sorunlar, engeller nelerdir?
Çavdar- Türk toplumunda bilim adamının kavram ve saygınlığı yeterince anlaşılamamıştır. Bilimi, toplumun değer yargıları içinde ve gündeminde en başta tutmak gerekir. Devlet zaman zaman bilim ve bilim araştırma kurumlarına pek de yakın olamamıştır. Ayrıca bilim adamlarının önünde bürokratik ekonomik ve hatta politik engeller bulunagelmiştir.

Soru : Ülkemizde bilime niçin önem ve öncelik verilmiyor?
Çavdar- Ülkemizde bilime yeterince önem ve öncelik verilmemesinin asıl nedeni, eğitim düzeyinin ve düzeninin bu yönde yapılanmamış olmasıdır. Kamuoyunun gündemini sürekli olarak politik, sportif ya da günlük trajik olaylar işgal etmektedir. Gençlerin önüne en yüce bir ideal olarak bilim konulamamıştır.

Soru: Bir bilim politikasının ana çizgileri neler olmalı?
Çavdar- Bilim politikasının başlıca öğesi özgün düşünme ve tartışma ortamının ve bilimsel kavramların tüm eğitim programlarında (ilkokuldan itibaren) egemen kılınmasıdır. Ülkemiz için bilimdeki önceliklerin saptanması ve gerektiğinde devlet katında önerilerde bulunması da öncelikler arasındadır.

Soru: TÜBA nasıl bir üyelik politikası izleyecek, kısa zamanda genişlemeyi düşünüyor musunuz?
Çavdar- TÜBA'nın üyelik koşulları, ilgili yasada ayrıntılarıyla belirtilmiştir. Bu hükümler çerçevesinde uluslararası bilime katkıda bulunulması ve bu katkıların bilim atıfları endekslerinde genel kabul ve yankı bulması üyelikte önemli bir kriter olacaktır. TÜBA'nın TÜBİTAK'tan ayrıcalığı sosyal bilimleri de çatısı altında toplamasıdır. TÜBA, çalışmasına başladıktan sonra yeni üyeler büyük bir titizlikte ve aşama aşama seçileceklerdir.

Soru: Yasal çerçevesi TÜBA'ya bilim politikasında yeterince yönlendirici bir etkinlik veriyor mu?
Çavdar- Yasal çerçevesi TÜBA'ya ülkenin bilim politikasında yönlendirici etki sağlayabilir. Bu bağlamda tüzük ve yönetmeliklerle TÜBA'nın etkinlikleri arttırılabilir.

Fotoğraf 5: Cumhuriyet Gazetesi Bilim-Teknik Eki'nden Sn. Orhan Bursalı ile Söyleşi, 1996

Arif İsmet Çetingil (1896-1985), Prof. Dr. Fritz Reimann (1897-1995), Prof. Dr. Muzaffer Aksoy (1915-2001), Prof. Dr. Şeref İnceman (1919-1994), Prof. Dr. Ayhan Çavdar (1930-), Prof. Dr. Burhan Say (1923-), Prof. Dr. Nail Tartaroğlu (1925-2005) ve Prof. Dr. Mustafa Karaca (1929-2001) tarafından kurulmuş olduğu görülmektedir (21).

Çavdar, 2000'li yılların ilk 15 yılında sağlık sorunlarıyla karşılaşmaya başladı. Öğrencisi olan Prof. Dr. Mehmet Haberal tarafından tedavi ve bakımı sağlandı ve Başkent Üniversitesi Hastanesi'nde tedavi gördü. Ancak, 89 yaşında, 24 Haziran 2019'da, tedavi gördüğü Başkent Üniversitesi Ankara Hastanesi'nde hayata veda etti. Çavdar için ilk tören, 28 Haziran Cuma günü Ankara Üniversitesi Tıp Fakültesi Morfoloji Binası'nda gerçekleştirildi (22,23).

Prof. Dr. Ayhan O. Çavdar'ın vefatından sonra, Uluslararası Pediatrik Onkoloji Derneği, Fransa'da düzenlediği *51th International Society Pediatric Oncology*-SIOP Kongresi'nde Çavdar'a ve aynı yıl kaybettiğimiz diğer önemli hekimlere uluslararası camia adına bir saygı duruşunda bulundu (Fotoğraf 6).

Çalışma Arkadaşları ve Öğrencilerinin Ayhan Çavdar ile İlgili Yazılarından Kesitler

Prof. Dr. Ayhan Çavdar'ın çalışma arkadaşları ve öğrencilerinin görüş ve izlenimleri, biyografisinin önemli bir parçasını oluşturmaktadır. Bu görüşler sayesinde, Prof. Dr. Çavdar'ın sadece bir akademisyen olarak değil, aynı zamanda bir insan olarak da kimliği ve kişiliği hakkında daha kapsamlı bilgi edinmek mümkün olmuştur.

Çalışma arkadaşlarına, Ayhan Çavdar'ın çok saygıdeğer ailesi vasıtasıyla ulaşılarak, yaşadıkları anılarla ilgili telefon görüşmeleri sırasında sorular yönlendirilmiş ve kendisiyle ilgili görüşlerini içeren bir yazı kaleme alıp almayacakları sorulmuştur. Aile bireyleri veya e-posta yoluyla ulaşılan Ayhan Çavdar'ın, bugün pek çoğu Prof. Dr. veya uzman

Fotoğraf 6: *51th Congress of the International Society Pediatric Oncology*-SIOP toplantısında o yıl vefat eden hocaların ekrana yansıtılarak anılması

doktor olan öğrencileri, konu ile ilgili bilgilendirilmelerinin ardından hocaları için birer mektup yazmayı kabul etmişlerdir. Çalışma arkadaşları gibi, bu yazılarını tarafıma e-posta yoluyla göndermişlerdir. Ayhan Hoca ile ilgili daha önce fikirlerini bildiren hocaların yazılarına aile arşivinden erişilmiş, hocalar tekrar aranarak kullanım izni sağlanmıştır.

Tek tek iletişime geçilip, kısa röportajlar yapılan Prof. Dr. Ayhan Çavdar'ın çok yakın dostları ve öğrencilerinin paylaşımlarından kesitler aşağıda verilmiştir. Paylaşımlar, metinlerin elimize ulaşma ve hocalarımızla görüşme tarih sırasına göre sıralanmıştır. Vefat eden hocalarımıza ait belge ve mektuplar aile arşivinden sağlanmıştır.

Hocamızın araştırma ve eğitimle geçen saygın yaşamı hepimize, özellikle de gençlere örnek olmalıdır.

Prof. Dr. Sevgi Gözdaşoğlu

Meslek yaşamımın her aşamasında büyük emeği olan Değerli Hocam Prof. Dr. Ayhan Çavdar'a saygılarımı sunuyor, sağlıklı bir ömür diliyorum.

Prof. Dr. Emel Babacan

Profesör Ayhan Çavdar: Akademisyenlikte İlk İdollerimden Biri...

Prof. Dr. Faik Sarıalioğlu

Ben bugün çocuk onkoloğu olduysam, ona hayranlığımdan oldum. İdolümdü, rol modelimdi. Huzur içinde uyusun!

Prof Dr Volkan Hazar

Örnek bir insan, örnek bir yurttaş, tıp alanında öncü bir "bilim kadını" ve daha fazlası ...

Dr. H. Bülent Önder

Prof. Dr. Ayhan Çavdar Hoca, Türkiye'nin genç, dinamik beyinleri için parlak ve iyi bir örnektir. Onun bilimci kişiliğini sorgulayarak, onu dinleyerek ve onu anlatıp tanıtarak, genç beyinlerimizi besleyebiliriz ve daha anlamlı alanlara yönlendirebiliriz.

Prof. Dr. Yücel Kanpolat

Bir gün bana "Gökhan Bey, sizin bugün saygı duyup imrendiğiniz liderler, size saygı duymaya ve imrenmeye başladıklarında kendinizi bir adım ileri gitmiş sayabilirsiniz" demişti. Bana böylesine yüksek bir eşik belirlediği için kendisine teşekkür ediyor ve onun bu önerisini gerçekleştirebilmek için çalışmaya devam ediyorum."

Prof. Dr. Gökhan Hotamışlıgil

Ayhan Öğretmen gerçek bir "Cumhuriyet" projesiydi.

Prof. Dr. Mustafa Çetiner

Yaptığı bilimsel çalışmalar ve hizmetler ile Bilim dünyasını ülkemizden en fazla aydınlatan bir bilim insanı olarak saygı ve minnetle anıyorum, ışıklar içinde uyusun...

Prof. Dr. Duran Canatan

Uzmanlığımı, kariyerimi, dolaylı olarak evliliğimi olumlu olarak etkileyen sevgili hocam rahmetli Prof. Dr. Ayhan

Okçuoğlu Çavdar'ın herkesce bilinen bilimsel kimliği yanında insani ve ahlaki kimliğiyle de nasıl bir "yüce dağ" olduğunu anlatmak mı? çok zor!

Prof. Dr. Metin Özenci

...

Başarılı bir meslek yaşamını özetleyerek genç bilim insanlarına değerli bir örnek olarak sunuyor, anısı önünde saygı ile eğiliyorum.

Yekta Güngör Özden/ Sözcü Gazetesi, 6 Nisan 2020

Prof. Dr. Ayhan Okçuoğu Çavdar ülkemizde yetişmiş üstün nitelikleri olan gerçek bir bilim kadınıydı. Onu tanımış olmaktan onur duyarım.

Prof.Dr. Orhan Öztürk

"Bu dünya bir pencere, bakan geçti" demişler. Hepimiz bu saptamanın içindeyiz, dışında kalabilen var mı? Yok ve olmayacak elbette. Ayhan hocam huzur içinde uyuyunuz.

Prof.Dr. Berna Arda

Atatürk'ün ışıklı yolunda kendini yetiştirmiş bir akademisyen..

Prof.Dr. Kürşat Yıldız

Tartışma ve Değerlendirme

Prof. Dr. Ayhan Çavdar, Türkiye'nin tıp dünyasında önemli bir kişilik olarak tanınır. Hem akademik alanda yaptığı çalışmalarla hem de TÜBA başkanlığı gibi önemli bir görevdeki liderliğiyle dikkat çeker. Ancak, onun bilimsel mirası ve akademik liderliği üzerine bir değerlendirme yapılırken, akademik kariyeri ve bilimsel çalışmaları yanında kan hastalıkları, özellikle de trombositler üzerine yaptığı araştırmalar ve çocuk hastalarında çığır açacak çalışmaları oldukça önemlidir. Bu çalışmalarla, ülkemizde çalışılmayan konulara eğilmiş, ülkemizdeki hastalık tiplerini ortaya koyarak coğrafya faktörünün sağlıkta ne denli önemli olduğunu kanıtlamıştır.

Ayhan Çavdar'ın çocuk hematolojisi ve onkolojisi alanındaki çalışmaları, özellikle çocuklarda yaygın olarak görülen kan hastalıkları ve kanserler üzerinde odaklanmıştır. Pika hastalığı ve çinko eksikliği gibi önemli sağlık sorunlarını tanımlaması ve bu konuda bilimsel araştırmalar yapması, Türkiye'de ve uluslararası alanda sağlık politikalarının şekillenmesine ve çocuk sağlığının iyileştirilmesine önemli katkılarda bulunmuştur. Prof. Dr. Çavdar, çocuklardaki çinko eksikliğinin gelişim geriliğine neden olduğunu ortaya koyarak, bu konuda sayısız kongre düzenlenmesine ve dünya bilim camiasında "Bayan Çinko" olarak anılmasına neden olmuştur.

Prof. Dr. Ayhan Çavdar'ın öğrencileri arasında yetiştirdiği birçok önemli bilim insanı ve akademisyen, onun bilgi birikimi ve öğretim yeteneğinin bir göstergesidir. Öğrenci yetiştirilmesine oldukça önem veren Prof. Dr. Ayhan Çavdar, hasta başı derslerinde ve vizitlerinde hastaları ile ilgilenmesinin yanında, öğrencilerinin olgulara katılımını oldukça önemsemiş; öğrencilerine etik değerler doğrultusunda "Dr. Hanım" ve "Dr. Bey" şeklinde seslenerek, özgüvenli birer hekim olmaları için çaba göstermiştir.

Kendisinin etik değerlere bağlılığı, etik dışı tüm olaylar karşısında sergilediği tavırlar ve hastalarına gösterdiği özen ve ilgi, onun tıp camiasında mesleki olarak ün kazanmasına sebep olmuştur. Ayrıca, bu özellikleri ona mesleğinde bir lider ve fikirlerine önem verilen bir hoca olma vasfını da sağlamıştır. İletişiminin kısıtlı olduğu insanlara karşı adaletli ve empatik tavırları, çoğu zaman karar mekanizmalarının içinde yer almasını sağlamıştır.

Prof. Dr. Ayhan Çavdar, Türkiye'de tıp alanında iz bırakan bir figür olmuş, hem bilimsel çalışmalarıyla hem de liderlik ve öğretim faaliyetleriyle önemli bir miras bırakmıştır. Onun çalışmaları, Türkiye'nin sağlık alanının gelişimine ve çocuk sağlığının iyileştirilmesine önemli katkılarda bulunmaya devam etmektedir.

Ayrıca, TÜBA'nın kuruluşunda ve yönetiminde üstlendiği liderlik rolü, ülkenin bilimsel ve akademik gelişimine büyük katkı sağlamıştır. TÜBA'nın ilk kadın başkanı olarak gösterdiği gayretle, bilimin ve akademik araştırmaların teşvik edilmesi ve yaygınlaştırılması için çaba göstermiştir. TÜBA'nın kuruluş aşamasında belirlediği hedeflere ulaşmayı amaçlayan Ayhan Çavdar, gerçekten de tüm dünyada TÜBA'nın anılmasını sağlamış, kadın bir başkan olarak yaptığı önemli atılımlarla dünyaya örnek teşkil etmiş, kadın üyelerin çokluğu ve bu kadınların Türkiye bilim camiasına verdikleri katkılarla dünya çapında yankı uyandırmıştır. Liderlik vasfı sayesinde TÜBA stratejik hedeflerine kolayca ulaşabilmiş, Akademi bu liderini ikinci kez seçerek bilime yönelik strateji ve politikalar geliştirmede kararlı olduğunu da ortaya koymuştur.

Sonuç

Sonuç olarak, çalışma hayatında bir lider olarak tanımlayabileceğimiz Prof. Dr. Ayhan Çavdar, Türkiye'de tıp alanında iz bırakan bir figür olmuş, hem bilimsel çalışmalarıyla hem de öğretim faaliyetleriyle gelecek nesillere önemli bir miras bırakmıştır. Hala yayınları bilimsel çalışmalarda referans gösterilen Ayhan Çavdar'ın bilimsel çalışmaları, diğer bilim insanlarını onun koyduğu temeller üzerine yenilerini araştırmaya yönlendirmekte; böylelikle Prof. Dr. Çavdar, Türkiye'nin sağlık alanının gelişimine ve çocuk sağlığının iyileştirilmesine önemli katkılarda bulunmaya devam etmektedir.

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SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Evaluation of Patients with Adnexal Masses in the Middle and Late Adolescent Age Group in a Tertiary Care Center

Üçüncü Basamak Bir Merkezde Orta ve Geç Adölesan Yaş Grubundaki Adneksiyel Kitleli Hastaların Değerlendirilmesi

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Abstract

Objectives: Although adnexal masses are an essential reason for gynecological surgeries in adolescents, early diagnosis and treatment are essential for preserving fertility. This study aimed to analyze the clinical features, treatment management, and histopathological results of patients with adnexal masses in a tertiary care center in the middle and late adolescent age group.

Materials and Methods: Adolescent patients with adnexal masses were evaluated retrospectively between January 2015 and December 2019. Patients were classified as middle (15-17 years) and late (18-21 years) adolescents. Patients' complaints, diagnoses, mass diameters and locations, treatment methods, surgery characteristics, and histopathological results were compared.

Results: A total of 141 patients in the middle adolescence (n=20) and late adolescence groups (n=121) were included in the study. Abdominal pain (70.9%), abdominal distension (11.3%), and menstrual disorders (7.1%) were the most common symptoms in the entire population. It was determined that 51.9% of the masses were benign neoplastic tumors, and 1.9% were malignant tumors. Surgery was not considered in 24.8% of the patients. Of the operated adolescents, 65% underwent laparoscopy, and 95.3% (n=101) underwent ovarian-preserving surgery. The most common histopathological diagnoses were benign serous cysts (18.9%), mature cystic teratoma (18.9%), and hemorrhagic cysts (17%). The laparoscopic surgery rate was significantly higher in the late adolescent group (p=0.024). The operated patients' average mass size was significantly higher (p<0.001).

Conclusion: The malignancy rate is low in patients with early and late adolescent adnexal masses. In the management of these patients, minimally invasive methods and ovarian protective interventions are essential in preserving fertility.

Keywords: Adnexal neoplasm, adolescent, fertility, laparoscopy, ovarian cancer

Öz

Amaç: Adneksiyel kitleler, adölesanlardaki jinekolojik cerrahilerin önemli bir sebebi olmakla birlikte erken tanı ve tedavi fertilitenin korunması açısından önemlidir. Bu çalışmanın amacı, üçüncü basamak bir merkezdeki orta ve geç adölesan adneksiyel kitleli hastaların klinik özelliklerini ve sonuçlarını analiz etmektir.

Gereç ve Yöntem: Ocak 2015 ile Aralık 2019 tarihleri arasında adneksiyel kitle nedeniyle takip edilen adölesan hastalar retrospektif olarak değerlendirildi. Hastaların şikayetleri, tanıları, kitle çapları ve yerleşimleri, tedavi yöntemleri, operasyonların özellikleri ve histopatolojik sonuçlar karşılaştırıldı.

Bulgular: Orta adölesan (n=20) ve geç adölesan grupta (n=121) toplam 141 hasta çalışmaya dahil edildi. Tüm popülasyonda karın ağrısı (%70,9), karında şişlik (%11,3) ve menstrüel bozukluklar (%7,1) en sık semptomlar idi. Kitlelerin %51,9'unun benign neoplastik tümör ve %1,9'unun malign

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tümör olduğu saptandı. Hastaların %24,8'inde operasyon düşünülmedi. Opere edilen adölesanların %65'ine laparoskopi, %95,3'üne (n=101) over koruyucu cerrahi uygulandı. En sık histopatalojik tanılar benign seröz kist (%18,9) ve matür kistik teratom (%18,9) ve hemorajik kist (%17) idi. Geç adölesan grupta laparoskopik cerrahi oranı anlamlı olarak yüksek saptandı (p=0,024). Opere edilen hastaların kitle boyutları anlamlı olarak yüksek saptandı (p<0,001).

Sonuç: Erken ve geç dönem adölesan adneksiyel kitleli hastalarda malignite oranı düşüktür. Adölesan adneksiyel kitleli hastaların yönetiminde minimal invazif yöntemler ve over koruyucu müdahaleler fertilitenin korunmasında önemlidir.

Anahtar Kelimeler: Adneksiyel neoplasm, adölesan, fertilite, laparoskopi, over kanseri

Introduction

Adolescence is defined as a period that begins with rapid biological and physical development, as well as sexual and psychosocial maturation, and in which the individual gains independence and social productivity. Adolescence is the transition period from childhood to adulthood. It is divided into periods such as early adolescence (10-14 years), middle adolescence (15-17 years), and late adolescence (18-21 years) according to developmental characteristics and health care needs (1). Adnexal masses may originate from the genital system, urinary, gastrointestinal tract, or retroperitoneal, depending on functional, congenital, inflammatory, and neoplastic processes. Although adnexal masses are rare in adolescents, they are the most common cause of gynecological surgery. Its incidence has been reported as 2.6 per 100 thousand (2). When planning the treatment of patients with adnexal masses, many factors such as age, menarche status, physical development, and malignant potential of the mass should be considered. Preserving the integrity of the ovarian tissue and other genital structures is extremely important for fertilization.

With the widespread use of ultrasonography (USG) in clinical practice, the frequency of detection of adnexal masses has increased. Most of these masses are simple cysts or corpus luteum cysts with a low potential for malignancy. The rarity of adnexal masses in adolescents, the low index of suspicion, and non-specific complaints can make diagnosis difficult (3-6). More information is needed regarding the histopathological structure of the existing mass for early diagnosis and management of adnexal masses in adolescents to protect fertilization and physiological development.

This study analyzes the clinical characteristics, treatment management, and histopathological results of patients with adnexal masses in a tertiary care center in middle and late adolescence.

Materials and Methods

This retrospective observational study was started by the principles of the Declaration of Helsinki after receiving approval from the University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinical Trials Review Board and Ethics Committee (date: 02.01.2023, approval no.: KAEK/2022.12.242). The study included patients in the middle (15-17 years) and late (18-21 years) adolescent age group who were followed up for adnexal mass at the University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital between January 2015 and December 2019. Patients under 15 and over 21 were excluded from the study.

The patient's age, symptoms, USG findings (adnexal mass size and side), laboratory findings (CA-125 level), treatment management, need for urgent surgery, the surgical procedure applied in operated patients, and histopathological results of the mass were recorded.

Adnexal masses were classified as non-neoplastic, neoplastic benign, and neoplastic malignant according to histopathological results and analyzed between groups. Study data were accessed retrospectively through the hospital information system and patient files. The patients were divided into mid-adolescent and late-adolescent, according to age range, and the study data were compared between the groups. Patients with adolescent adnexal masses were also analyzed by classifying them into expectant and surgery groups according to the need for surgery.

The sample size was not determined in this retrospective descriptive study in which we evaluated adnexal masses in early and late adolescents. All patients who met the inclusion criteria during the five years were included in the study.

Statistical Analysis

SPSS 26.0 program (SPSS Inc., Chicago, USA) was used to analyze the data. Data are expressed as mean, standard deviation, number of patients, and percentage. The conformity of the variables to the normal distribution was evaluated analytically (Shapiro-Wilks test) and visually (histogram). Independent samples t-test was used to analyze quantitative data with normal distribution among the groups, and the Mann-Whitney U test was used to analyze quantitative variables that did not show normal distribution. The Pearson chi-square and Fisher's exact tests were used to evaluate qualitative data. The statistical significance level was accepted as $p<0.05$.

Results

A total of 141 patients were included in the study: 20 (14.1%) in the middle adolescence group and 121 (85.9%) in the

late adolescence group. The mean age of the entire population was 19.5±1.7 (15-21) years. While 24.8% (n=35) of the patients were followed up without surgery, surgery was performed in 75.2% (n=106). Laparoscopy was performed in 65.1% (n=69) of the operated patients, and laparotomy was performed in 34.9% (n=37). The rate of laparoscopic surgery in the late adolescence group was significantly higher than in the early adolescence group (p=0.024). While the average diameter of adnexal masses in the entire population was 5.8±2.5 (range, 2-14) cm and the average carbohydrate antigen (CA)-125 level was 21±14.6 (range, 4-90) U/mL, no significant difference was detected between the groups (p=0.880 and p=0.578, respectively). The most common complaints in adolescents with adnexal masses were abdominal pain (70.9%), abdominal swelling/palpable mass (11.3%), and menstrual irregularity (7.1%) and swelling (70.9%) (Table 1).

In patients with adnexal masses who underwent surgery, 51.9% (n=55) had benign neoplastic tumors, 46.2% (n=49) had non-neoplastic tumors, and 1.9% (n=2) had malignant tumors. One of the patients with malignant tumors was 17 years old (anaplastic large cell lymphoma), and the other was 20 years old (dysgerminoma). Both patients had abdominal pain, and a mass was detected on the left side. Unilateral salpingo-oophorectomy was performed in both patients. No significant difference in mass characteristics was observed between the groups (p=0.069). Although the rate of emergency surgery in the late adolescent group was higher than in the mid-adolescent group, no significant difference was detected (63.3% vs. 36.7%, p=0.052). The most frequently performed surgical operations were cystectomy (57.5%), detorsion (26.4%), and cyst aspiration (10.4%). The operations performed were similar between the groups (p=0.189) (Tables 2 and 3).

When patients with adnexal masses were classified according to whether they had undergone surgery, their diameter was significantly higher in the surgery group (6.3±2.6 vs. 4.2±1.4 cm, p<0.001). Additionally, the complaint of abdominal pain was found to be significantly higher in patients who underwent surgery (84% vs. 31.4%, p<0.001) (Table 4).

Discussion

This study investigated patients with adnexal masses in the middle and late adolescence age group. It found that the majority of adnexal masses were benign neoplastic tumors (such as benign serous cysts and mature cystic teratoma) and non-neoplastic tumors (hemorrhagic cysts), and the rate of malignant tumors was low. It was determined that laparoscopic surgery was performed at a significantly higher rate in the late adolescent age group. In addition, ovarian-sparing surgery was performed at a rate as high as 95% in all adolescents.

Table 1: Clinical characteristics of patients

	Overall (n=141)	Middle adolescent (n=20)	Late adolescent (n=121)	p-value
Age (years)	19.5±1.7 (15-21)	16.2±0.9 (15-17)	20.1±1.1 (18-21)	-
Clinical presentation				0.514
Abdominal pain Abdominal mass Dysmenorrhea Nausea/vomiting Incidental	100 (70.9) 16 (11.3) 10 (7.1) 9 (6.4) 6 (4.3)	13 (65) 4 (19) 1 (5) 2 (10) 1 (4.8)	87 (71.9) 12 (10) 9 (7.4) 7 (5.8) 5 (4.2)	
Tumor size (cm)	5.8±2.5 (2-14)	5.4±1.8 (3-9)	5.8±2.7 (214)	0.880
Tumor size range				0.404
<5 cm 5-10 cm >10 cm	55 (39) 78 (55.3) 8 (5.7)	7 (35) 13 (65) 0	48 (39.7) 65 (53.7) 8 (6.6)	
Expectant	35 (24.8)	4 (20)	31 (25.8)	0.507
Surgery	106 (75.2)	16 (80)	90 (74.3)	**0.024**
Laparoscopy Laparotomy	69 (65.1) 37 (34.9)	7 (41.2) 10 (58.8)	62 (69.7) 27 (30.3)	
CA-125 (U/mL)	21±14.6 (4-90)	19.0±12.3 (6-49)	21.4±15.0 (4-90)	0.578
Side				0.913
Right Left Bilateral	74 (52.5) 58 (41.1) 9 (6.4)	10 (50) 9 (45) 1 (5)	64 (52.9) 49 (40.5) 8 (6.6)	

Data are given as mean ± standard deviation (range), number of patients and percentage

Table 2: Characteristics of patients undergoing surgery				
	Overall (n=106)	**Middle adolescent (n=16)**	**Late adolescent (n=90)**	**p-value**
Diagnosis				0.069
Benign neoplastic tumor	55 (51.9)	12 (70.6)	43 (48.3)	
Non-neoplastic tumor	49 (46.2)	4 (23.5)	45 (50.6)	
Malignant tumor	2 (1.9)	1 (5.9)	1 (1.1)	
Operation method				0.052
Emergency	63 (59.4)	6 (37.5)	57 (63.3)	
Elective	43 (40.6)	10 (62.5)	33 (36.7)	
Types of surgery				0.189
Cystectomy	61 (57.5)	11 (64.7)	50 (56.2)	
Detorsion	28 (26.4)	3 (17.6)	25 (28.1)	
Cyst aspiration	11 (10.4)	1 (6.3)	10 (11.1)	
Salpingo-oophorectomy	3 (2.8)	2 (12.5)	1 (1.1)	
Oophorectomy	2 (1.9)	0	2 (2.2)	
Abscess drainage	1 (0.9)	0	1 (1.1)	
Data are given as number of patients and percentage				

Table 3: Histopathological results			
	Overall (n=106)	**Middle adolescent (n=16)**	**Late adolescent (n=90)**
Benign neoplastic tumor			
Benign serous cyst	20 (18.9)	4 (25)	16 (17.8)
Mature cystic teratoma	20 (18.9)	4 (25)	16 (17.8)
Serous cystadenoma	11 (10.4)	3 (18.8)	8 (8.9)
Serous cystadenofibroma	2 (1.9)	0	2 (2.2)
Mucinous cystadenofibroma	2 (1.9)	0	2 (2.2)
Non-neoplastic tumor			
Hemorrhagic cyst	18 (17)	2 (12.5)	16 (17.8)
Paratubal cyst	11 (10.4)	0	11 (12.2)
Endometrioma	7 (6.6)	0	7 (7.8)
Corpus luteum	7 (6.6)	2 (12.5)	5 (5.6)
Follicle cyst	3 (2.8)	0	3 (3.3)
Paraovarian cyst	1 (0.9)	0	1 (1.1)
Theca cell tm	1 (0.9)	0	1 (1.1)
Tubo-ovarian abscess	1 (0.9)	0	1 (1.1)
Malignant tumor			
Dysgerminoma	1 (0.9)	0	1 (1.1)
Anaplastic large cell lymphoma	1 (0.9)	1 (6.3)	1 (1.1)
Data are given as number of patients and percentage			

Clinical signs and symptoms vary in adolescents with adnexal masses. Clinical symptoms such as abdominal pain or pelvic pain, a mass in the abdomen or pelvic area, menstrual irregularities, and nausea/vomiting may be observed. Sometimes, it can be diagnosed incidentally without causing any complaints. Additionally, since ovarian pathologies are rarely encountered in adolescents, non-specific symptoms such as acute abdominal pain may suggest more common pathologies such as acute appendicitis. For this reason, it may be difficult to diagnose patients. In the literature, the most common presenting complaint of adolescents with adnexal masses has been reported as abdominal pain (56-87%) (7,8). Other frequently reported symptoms are abdominal swelling-palpable mass (6.7-10.2%), menstrual disorders (3-10.2%), and nausea/vomiting (3.4-4.7%) (7-9). In our study, consistent with the literature, the most common symptoms in the patients were abdominal pain (70%), abdominal swelling/palpable mass (11.3%), and menstrual disorders (7.1%). In addition, in this study, a significantly higher rate of abdominal pain complaints was detected in patients who underwent surgery compared to the observed patients.

Adnexal masses are rare in the adolescent age group. Due to irregular menstruation and frequent anovulation, most of these masses are non-neoplastic ovarian cysts, including follicular cysts, corpus luteum, and theca lutein cysts. Although

Table 4: Clinical characteristics of expectant and surgery groups			
	Expectant group (n=35)	**Surgery group (n=106)**	**p-value**
Age (years)	19.6±1.5 (16-21)	19.5±1.8 (15-21)	0.972
Clinical presentation			**<0.001**
Abdominal pain Abdominal mass Dysmenorrhea Nausea/vomiting Incidental	11 (31.4) 13 (37.1) 10 (28.6) 1 (2.9) 0	89 (84) 3 (2.8) 0 8 (7.5) 6 (5.7)	
Tumor size (cm)	4.2±1.4 (2-8)	6.3±2.6 (2-14)	**<0.001**
Tumor size range			**<0.001**
<5 cm 5-10 cm >10 cm	23 (65.7) 12 (34.3) 0	32 (30.2) 66 (62.3) 8 (7.5)	
CA-125 (U/mL)	23±16 (6-75)	20.4±14.2 (4-90)	0.466
Side			0.963
Right Left Bilateral	18 (51.4) 15 (42.9) 2 (5.7)	56 (52.8) 43 (40.6) 7 (6.6)	
Data are given as mean ± standard deviation (range), number of patients and percentage			

spontaneous resolution is often observed, surgical treatment is required in approximately 25% of cases due to persistence (10). USG is often sufficient for the diagnosis of follicular cysts. Benign neoplasms are more common than malignant neoplasms. The most common types of benign neoplasms include mature teratomas, mucinous and serous cystadenomas, and endometriomas (11). Sükür et al. (9) reported that 67% of adolescent adnexal masses were non-neoplastic tumors, and 20.3% were benign neoplastic tumors. The authors stated that the most common non-neoplastic tumors are follicular cysts and corpus luteum cysts, while benign neoplastic tumors are frequently detected as mature teratoma and cystadenoma. Kang et al. (8) reported that adnexal masses were more common on the right side; 53% were benign neoplastic, 35% were non-neoplastic, and 7 were malignant tumors. The authors stated that among non-neoplastic tumors, corpus luteum cysts are more frequently detected in the middle adolescence age group, and endometriosis is more frequently detected in the late adolescence age group. In addition, they emphasized that mature cystic teratoma in benign neoplastic tumors is detected more frequently in both middle and late adolescence. In our study, consistent with the literature, more than half of the adnexal masses (51.9%) were detected as benign neoplastic tumors and were localized on the right side. While follicular cysts were most frequently detected among non-neoplastic tumors, benign serous cysts and mature cystic teratoma were most frequently detected among benign neoplastic tumors.

Malignant ovarian tumors constitute only 0.9% of all childhood and adolescence malignancies (12). Unlike adults, approximately 80% of malignant ovarian tumors are germ cell tumors. Although USG images of germ cell tumors vary, they can be distinguished from dermoid cysts due to the teeth, hair, and fatty tissues found within them. The second most common neoplastic tumors seen in adolescents are epithelial neoplasms, and their incidence increases with increasing age (13,14). The two most common types are serous and mucinous tumors. Kang et al. (8) reported that 7.8% of adnexal masses in children and adolescents were detected as malignant tumors (non-epithelial ovarian malignant neoplasms and borderline malignant tumors). Studies from tertiary centers in Türkiye reported that malignant tumors were detected in 0.9-11.8% of patients with adolescent adnexal masses (7,9,15). In our study, consistent with the literature, malignant tumors were detected in 1.9% (n=2) of patients with adolescent adnexal masses (dysgerminoma and anaplastic large cell lymphoma).

Various methods are used to diagnose adnexal masses and determine treatment. Most masses are detected using USG, the first-line imaging test (10,16). USG is a valuable diagnostic tool in distinguishing adnexal masses due to its easy accessibility, cost-effectiveness, and high diagnostic accuracy. USG findings can also provide helpful information about whether the patient needs surgery or conservative treatment (17). In addition, USG can enable continuous imaging and follow-up of relatively small ovarian masses without surgical treatment (18). The literature has stated that most simple cysts, whose size is 5-7 cm on USG, decrease in size or improve during follow-up (19). Kang et al. (8) reported that patients with adnexal masses who underwent surgery (50%) had larger tumors than those who were followed up without surgery (50%), neoplastic features were detected on USG, and in addition, the USG diagnosis was consistent with the histopathological diagnosis.

In addition to USG, computed tomography (CT) or magnetic resonance imaging (MRI) can also help diagnose malignant ovarian tumors. Additional information, such as the nature of the adnexal mass and metastatic involvement of pelvic and para-aortic lymph nodes, can be determined by CT or MRI. In our study, USG was used as the first method in diagnosis in all patients with adnexal masses. Computed tomography or MRI are auxiliary imaging methods when malignancy is suspected. Surgery was not performed in 24.8% of the patients, and they were followed up. Consistent with the literature, the mass sizes of the patients in the surgery group were significantly higher than in the follow-up group. Although many tumor markers such as human α-fetoprotein , β-hCG, CA-125, CA-19-9, and carcinoembryonic antigen are used in the follow-up of malignant ovarian tumors, their levels have been reported to be expected in approximately 50% of malignant tumors (20). In their same study, Kang et al. (8) reported that serum tumor markers were at normal levels in 44% of patients with adnexal masses. Therefore, normal serum tumor marker levels cannot exclude malignancy. In our study, CA-125 levels were analyzed as a tumor marker. Consistent with the literature, the CA-125 level was average in one of the patients with malignant neoplasm (middle adolescent group, diagnosed with anaplastic large cell lymphoma). In contrast, the CA-125 level was high in the other group (late adolescent group diagnosed with dysgerminoma). No significant difference was detected between middle and late adolescence age groups.

The standard treatment for benign ovarian tumors that are not considered malignant is ovarian-sparing surgery (21). A conservative approach should be applied as much as possible in order to preserve fertilization. Cystectomy and detorsion of the torsioned mass are usually performed using minimally invasive surgical methods (laparoscopic or robotic surgery). Ovarian-sparing surgery has been reported to have a low recurrence rate and high clinical success (22). Kang et al. (8) reported that 87% of patients with adnexal masses underwent ovarian-sparing surgery, and no patient required laparotomy. Pekcan et al. (15) reported that 94% of adolescents with adnexal masses underwent laparoscopy, and 1% of the patients underwent laparotomy. Dağdeviren et al. (7) reported that 67% of the patients underwent laparoscopy, and 28% underwent laparotomy after laparoscopy. The authors also emphasized that torsion was detected in 1/3 of the patients, and successful treatment was achieved with detorsion except for one of the patients. In our study, laparoscopy was performed in 65% of the patients who underwent surgery, while no patients underwent laparotomy after laparoscopy. Ovarian-sparing surgery was performed in 95.3% (101/106) of the operated patients. The fact that the pediatric surgery clinic decides on laparoscopy or laparotomy in some patients in the middle adolescence age group is influential in determining the lower rates of laparoscopic surgery in patients in the middle adolescence age group compared to the literature. However, our ovarian-preserving surgery rates were found to be similar to the literature.

Study Limitations

The study has some limitations. First, it is a single-center and retrospective study. Second, tumor markers other than CA-125 in adolescents with adnexal masses were not analyzed. Third, it could not be determined to what extent auxiliary methods such as CT and MRI, which were used in diagnosing all patients other than USG, were used in the diagnosis.

Conclusion

In conclusion, patients with adnexal masses in the early and late adolescence age group often experience abdominal pain, abdominal distension, and menstrual disorders. Most of these patients have benign neoplastic tumors and non-neoplastic tumors, but malignant tumors are rare. Recognizing rare adnexal masses in adolescent patients, monitoring them with conservative treatment when appropriate, and planning ovarian-preserving surgeries with minimally invasive methods when necessary are essential in preserving fertility.

Ethics

Ethics Committee Approval: The study was started by the principles of the Declaration of Helsinki after receiving approval from the University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinical Trials Review Board and Ethics Committee (date: 02.01.2023, approval no.: KAEK/2022.12.242).

Informed Consent: Consent was not obtained since it was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ç.A., Concept: H.Ç.A., K.A., Design: H.Ç.A., K.A., Data Collection and/or Processing: H.Ç.A., K.A., Analysis and/or Interpretation: H.Ç.A., K.A., Literature Search: H.Ç.A., K.A., Writing: H.Ç.A., K.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Management of Caustic Esophageal Injury: A Survey Study in Türkiye and Review of the Literature

Kostik Özofagus Yaralanmasının Yönetimi: Türkiye'de Bir Anket Çalışması ve Literatürün Gözden Geçirilmesi

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Abstract

Objectives: Management of caustic ingestion (CI) and esophageal burns are a serious problem which causes a significant burden on the health care services. Since absence of evidence-based guidelines optimal management of CI is still yet to be determined. The study aims to evaluate clinical approach of Turkish pediatric surgeons to caustic esophageal burns.

Materials and Methods: The survey questions were prepared through a literature review for controversial issues. The survey was sent to 450 member of Turkish association of pediatric surgery via Google Forms and 106 of them responded.

Results: There were 46 (43%) participants who do not perform endoscopy in whether symptomatic or asymptomatic patients in the first apply. Sixty (56%) participants preferred to perform endoscopy at the first apply. Thirty-six (34%) of participants perform endoscopy in case of certain ingestion of caustic substance, 14 (13.5%) perform in only symptomatic patients and 10 (9.5%) perform endoscopy in any suspicion of caustic ingestion. Seventy-one (67%) of the participants declared that they do not use antibiotics routinely and forty-six (45%) stated that they do not use steroids with or without esophageal burns.

Conclusion: Although some studies on CI management have been published, a clear algorithm in management of CI has not established yet. Clinicians tend to determine different follow-up and treatment algorithms based on clinical customs and their experience.

Keywords: Caustics, endoscopy, esophageal stricture

Öz

Amaç: Kostik alımı ve özofagus yanıklarının tedavisi, sağlık hizmetleri üzerinde önemli bir yük oluşturan ciddi bir sorundur. Kanıta dayalı kılavuzların bulunmaması nedeniyle kostik alımının optimal yönetimi henüz belirlenmemiştir. Çalışma, Türk çocuk cerrahlarının kostik özofagus yanıklarına klinik yaklaşımını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Anket soruları tartışmalı konulara ilişkin literatür taraması yoluyla hazırlanmıştır. Anket, Türkiye Çocuk Cerrahisi Derneği'nin 450 üyesine Google Formlar aracılığıyla gönderildi ve 106'ı yanıt verdi.

Bulgular: İlk başvuruda semptomatik veya asemptomatik hastalara endoskopi yapmayan 46 (%43) katılımcı vardı. Altmış (%56) katılımcı ilk başvuruda endoskopi yapmayı tercih etti. Katılımcıların 36'sı (%34) kesin kostik madde alımı durumunda endoskopi yaparken, 14'ü (%13,5) sadece semptomatik hastalarda, 10'u (%9,5) herhangi bir kostik madde alımı şüphesi varsa endoskopi yapıyor. Katılımcıların 71'i (%67) rutin olarak antibiyotik kullanmadığını, 46'sı (%45) özofagus yanığı olsun ya da olmasın steroid kullanmadığını belirtti.

Sonuç: Kostik alımı yönetimine ilişkin bazı güçlü çalışmalar yayınlanmış olmasına rağmen, yönetimi konusunda net bir algoritma henüz oluşturulmamıştır. Klinisyenler klinik geleneklere ve deneyimlerine göre farklı takip ve tedavi algoritmaları belirleme eğilimindedir.

Anahtar Kelimeler: Kostik madde, endoskopi, özofagus darlığı

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Introduction

Management of caustic ingestion (CI) and esophageal burns are a serious problem which causes a significant burden on the health care services (1-3). Initial admission of CI may be only suspicion of ingestion or symptomssuch as oropharyngeal or chest pain, dysphagia, vomiting, drooling, stridor, fever and even shock (1,4). Even though CI and esophageal burns are still relatively common in some countries such as Turkey, due to absence of evidence-based guidelines optimal management is still yet to be determined (5-7). Diagnostic role of endoscopy and its timing, steroid and antibiotic usage, type and timing of dilation of strictures are controversial and all of these vary between centers (1,2). The management solely depends on the experience of the surgeons and clinicalcustoms.

The study aims to evaluate clinical approach of Turkish pediatric surgeons (PSs) to caustic esophageal burns while emphasizing on endoscopy preference via an online questionnaire.

Materials and Methods

The survey questions were prepared through a literature review for controversial issues. Zargar et al. (8) classification was used to define grade of esophageal injury in the questions and its explained to clinicians in survey (Table 1). There is 21 questions. All participants questioned about their experience. While asking the preferneces of surgeons, it has been checked that they had the all facilities and they prefer one of them. Due to prevent any confusion, it was stated that the questions must be answered for children who was hemodynamically stable and there were no suspected esophageal or gastric perforation. The survey was sent to 450 member of Turkish association of pediatric surgery via Google Forms and 106 of them responded. Ethical approval was obtained from the Human Research Ethics Committee of Ankara University Faculty of Medicine (date: 26.03.2020, decision no.: İ3-182-20). Since the study did not include patients, patient consent was not obtained.

Table 1. Endoscopic clasiffication of esophageal caustic injuries, by Zargar et al.[4,8]

Grade	Description
Grade 0	Normal
Grade 1	Mucosal edema and hyperemia
Grade 2A	Superficial ulcerations, erosions, exudates
Grade 2B	Deep discrete or circumferential ulcerations
Grade 3A	Focal necrosis
Grade 3B	Extensive necrosis
Grade 4	Perforations

Statistical Analysis

No further statistical study was used. Surgeons' choices are shown in tables and percentages.

Results

A hundred and six PSs answered the survey. Forty (37.7%) of them had more than 16 years of experience in pediatric surgery. Nearly half of the participants (n=52, 49%) were affiliated with university hospitals, followed by those in education and research hospitals (n=26, 26.5%), state hospitals (n=19, 18%), and private hospitals (n=9, 8.5%). There were 46(43%) participants who do not perform endoscopy in whether symptomatic or asymptomatic patients in the first apply. Sixty (56%) PSs preferred to perform endoscopy at the first apply. Thirty-six (34%) of participants perform endoscopy in case of certain ingestion of caustic substance, 14 (13%) perform in only symptomatic patients and 10 (9%) perform endoscopy in any suspicion of CI (Table 2). Among the participants who performed endoscopy at the first apply, 51 (85%) stated that they perform endoscopy in the first 48 hours, 9 (15%) stated that they performed endoscopy within 48-96 hours after the application. Seventy-one (67%) of the participants declared that they do not use antibiotics routinely. Forty-six PS (45%) stated that they do not use steroids with or without esophageal burns (Figure 1). Sixteen (15%) of participants preferred routine usage of steroid in caustic esophageal burns and 42(40%) stated steroid usage in particular patients. Among PSs who do not perform endoscopy

Table 2. Endoscopy preference of participant

Endoscopy at first admission		
Yes, n=60 (57%)	No, n=46 (43%)	
Any suspicion of CI n=10 (9.5%)	Certain caustic ingestion n=36 (34%)	Symptomatic patients n=14 (13.5%)

CI: Caustic ingestion

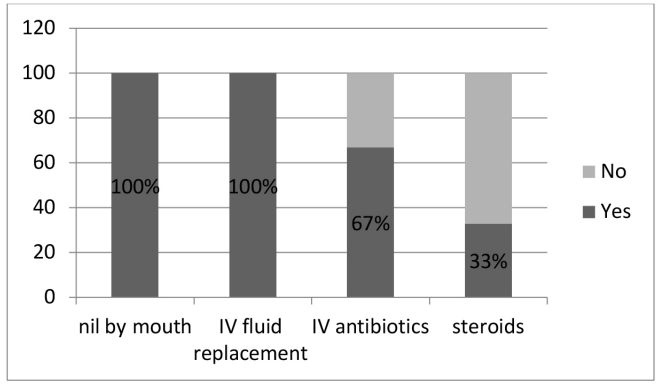

Figure 1: Routine medical treatment in caustic burns

IV: Intravenous

at first admission, 41 (89%) of them preferred endoscopy three weeks later in case of symptomatic esophageal stricture and three (9%) preferred routine endoscopy in all cases.

Sixty-two PSs (68.5%) stated that they perform further examination in follow-up only in symptomatic patients, 22 (20.8%) in patients who had Grade 2B and more serious burns in the first endoscopy. Twenty-two PSs (20.8%) preferred performing further examination in all CI cases. Participants preferred endoscopy (64%), upper gastrointestinal contrast study (UGCS) (11%) and both endoscopy and UGCS (25%) during follow-up. Eighty-five percent of PSs stated that planned examination timing was three weeks.

The participants preferred balloon dilation (57.5%), wire-guided rigid dilator (57.7%) for dilation in esophagealstrictures. Detailed information is shown in Table 3. The most common esophageal replacement method was colonic interposition (53%) followed by gastric transposition (30.9%), gastric tube transposition (9.6%).

Discussion

The present study revealed that there are many different approaches in CI among the Turkish PSs. The main debate was in requirement of endoscopic evaluation of esophagus following CI at the admission. Almost half of the participants stated that they do not perform endoscopy in early period after CI even in symptomatic patients.

Despite there are some studies which investigate the effectiveness of computed tomography, endoscopic ultrasound and scintigraphy, upper gastrointestinal tract endoscopy remains the gold standard to evaluate caustic injury of the esophagus (1,3,9,10). Endoscopy is also accepted as an important tool for prediction of prognosis and management and it reduces length of hospital stay in children without esophageal burn (1,3). Lamireau et al. (11) and Betalli et al. (12) reported that no severe esophageal injury or esophageal stenosis were occurred in asymptomatic children in their series and they argued endoscopy may not be necessary in these patients.

Aforementioned studies suggested performing endoscopy in all symptomatic patients (11,12). Interestingly, in the present study, 46 participants (43%) stated that they do not perform endoscopy in any patients but only children who has symptomatic esophageal stricture in follow-up period. These participants' approach was nil by mouth and intravenous fluid replacement until patient's symptoms such as drooling resolved.

Endoscopy timing is also a controversial issue in CI (1). There are no controlled studies which compare early (within first 24-48 hours) and late (48-96 hours) endoscopy (1). Zargar et al. (8) reported that delayed endoscopy at 48-96 hours after ingestion is safe and they reported no complication. However, current studies suggest that performing endoscopy early in CI is safe and complication concerns such as perforation during endoscopy consist on no scientific reasons (3,9,13). Endoscopy also identify patients without esophageal burn who can be discharged, therefore it may prevent prolongation of unnecessary hospitalization (3,14). Abbas et al. (14) reported that early endoscopy reduces length of hospital stay and treatment cost in a nationwide study (14). In the present study, 51 (85%) of participants who perform endoscopy in the first apply, preferred performing endoscopy first 48 hours.

Prognosis of CI has been found related to findings in endoscopic evaluation (1,2,15). Grade 1 and 2A esophageal burns rarely causes esophageal strictures (2,15). Patients with Grade 2B and Grade 3 esophageal burns develop esophageal stricture formation 70-100% of the cases (1). Additionally, degree of the esophagealinjury at endoscopy was found related to systemic complications and these findings may indicate emergency surgery (9).

The routine use of antibiotics is another controversial issue in CI management (1). In the literature, there is no strong evidence suggesting that antibiotic using reduces esophageal stricture formation (1,3,16,17). Hugh and Kelly (3) suggested that broad-spectrum antibiotics should be given all patients with second or third degree esophageal burns (3). In a comprehensive review,

Table 3. Participants preferance in esophageal dilation

Dilation method	Flouroscopy usage during the procedure	Topical agent application	Patient selection in topical agent application Total answer: 58
Rigid dilator with guide n=61 (57.5%)	No n=35 (33%)	No n=64 (60.4%)	Recurrent esophageal strictures n=51 (88%)
Balloon dilation n=61 (57.5%)	Routine n=51 (48.1%)	Steroids n=41 (38.7%)	At first esophageal dilation procedure n=4 (7%)
Rigid dilator without guide n=9 (8.5%)	In particular cases n=20 (18.9%) (History of complicated dilation, under one year of age and first dilation)	MMC n=15 (14.2%)	At first endoscopy following CI n=3 (5%)
Esophageal stent n=4 (3.8%)			

Abbreviation: CI: Caustic ingestion, MMC: Mitomycin-C

Bird et al. (1) recommended using antibiotics for children who are using steroids for airway damage and suspected mediastinal and lung involvement. In this survey, seventy-one (67%) of the participants declared that they do not use antibiotics routinely.

Based on their potential to decrease inflammation and fibrosis; corticosteroids are used for prevention of esophageal stricture development in CI (18). However, steroids have been reported ineffective to prevent stricture formation in several studies (18-20). Steroid usage has been reported to benefit patients with airway involvement, such as larynx edema, and it should be administered in these cases rather than all patients with CI (9,18,20). The present study reveal that 16 of participants (15%) use steroids routinely in CI.

Esopageal strictures are the most common late complication after CI (1). Surgical treatment of the esophageal strictures in children has evolved to non-surgical treatments (esophageal bougienage, balloon dilation) by years. (21). There is still no consensus regarding to use of esophageal dilation technique (22). In a meta-analysis, Josino et al. (23) compared esophageal bougienage (Savary dilator) and balloon dilation in benign esophageal strictures and they reported no differences between two techniques in terms of effectivity and complications. In this survey, the most preferred techniques were rigid dilator with guide-wire and balloon dilation. Rigid dilator without guide-wire and stent were preferred by some participants (8.5% and 3.8% respectively).

Local use of corticosteroids such as triamcinolone and betamethasone may be performed in esophageal strictures during the dilation procedure (24-26). Kochhar and Makharia (27) reported outcomes of topical steroid injection in 29 patients who suffer from esophageal strictures due to CI. According to their study, steroid injection reduces number of dilation and improves dysphagia scores (27). Camargo et al. (28) compared saline versus triamcinolone injection in caustic esophagus strictures in their randomized controlled study and found no difference between the groups in dilation number and dysphagia scores. However, larger luminal diameter obtained in steroid group significantly (28). Mitomycin-C (MMC) is another agent that can be used in esophageal strictures based on its property of inhibiting fibroblast proliferation (29). Ghobrial and Eskander (30) reported that MMC application associated with more symptomatic and endoscopic improvement and lower numbers ofdilation requirement compared to control group in refractory caustic-induced long segment esophageal strictures . Despite encouraging and promising reports in both triamcinolone and MMC usage in esophageal strictures, definition of the refractory stenosis, patient selection, application doses of both agent, number of applications have been reported differently in the literature (24,27,30-32).

Although the main approach is preserving patient's own esophagus in the management of esophageal strictures, esophageal replacement may be unavoidable in particular patients (33). Esophageal replacement traditionally can be performed by colonic or jejunal interposition, gastric tube interposition, gastric transposition (34,35). None of these methods are perfect and behave like a native esophagus (34). While colonic interposition is associated with higher risk of redundancy, anastomosis leakage and stricture, gastric transposition has higher respiratory morbidity and delayed gastric emptying (35). In the present study, the most preferred esophageal replacement method was colonic interposition, followed by gastric transposition and gastric tube interposition.

Study Limitations

This study has several limitations. Response bias may significantly influence the results, as the questionnaire was distributed to members of the Turkish Association of Pediatric Surgery, potentially skewing responses toward surgeons who are more engaged in academic meetings. Additionally, the survey was not sent to pediatric gastroenterologists, which represents another limitation.

Conclusion

There are many controversial issues in CI. Although some studies on CI management have been published, a clear algorithm in CI management has not established yet. Clinicians tend to determine different follow-up and treatment algorithms based on customs and their clinical experience as it may be seen in the present study. Prospective controlled studies are required to reach a consensus.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Human Research Ethics Committee of Ankara University Faculty of Medicine (date: 26.03.2020, decision no.: İ3-182-20).

Informed Consent: The study did not include patients, patient consent was not obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., D.İ., G.G., U.A., Concept: S.S., D.İ., E.E., Design: E.E., G.G., A.M.Ç., Data Collection and/or Processing: D.İ., U.A., Analysis and/or Interpretation: D.İ., A.M.Ç., U.A., Literature Search: D.İ., E.E., A.M.Ç., U.A., Writing: S.S., D.İ., U.A.

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SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Fibrinogen-Albumin Ratio: A Potential New Marker for Gestational Diabetes Severity?

Fibrinojen-Albümin Oranı: Gestasyonel Diyabet Şiddeti için Potansiyel Yeni Bir Belirteç Olabilir mi?

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Abstract

Objectives: Approximately 15% of all pregnancies result in gestational diabetes mellitus (GDM). GDM is a common metabolic disease that is associated with significant changes in inflammatory markers and insulin sensitivity. Higher fibrinogen and lower albumin levels are observed during pregnancy. In addition, since GDM is also an inflammatory process, the fibrinogen-albumin ratio (FAR) may increase more than that in normal pregnancies, suggesting a potential role as an indicator of disease severity. The article aims to investigate the relationship between the severity of gestational diabetes (GDM) and the FAR.

Materials and Methods: A prospective observational study was conducted at the Giresun Maternity and Children Training and Research Hospital. This study included 87 pregnant women, 41 women with GDM, and 46 women in the control group. Demographic, clinical, and biochemical parameters were collected, and FAR was computed. Statistical analyses were conducted to evaluate the diagnostic efficacy of FAR and compare the groups.

Results: Compared to the control group, the GDM group had significantly higher fibrinogen levels (440±73.8 mg/dL vs. 403±57.9 mg/dL, p=0.012), lower albumin levels (36.61 vs. 38.80 g/L, p<0.001), and a higher FAR (12.28 vs. 10.07, p<0.001). A weak positive correlation was found between estimated fetal weight and FAR (p=0.04, r=0.22). ROC analysis demonstrated that FAR had an area under the curve of 0.810, a sensitivity of 78%, and a specificity of 71.7%, indicating acceptable diagnostic accuracy for GDM.

Conclusion: In this study, pregnant women with GDM showed a significant increase in FAR, and this elevation correlated with fetal growth. The results of the study support the potential of FAR as a new biomarker in the management of GDM. However, further research is needed for these findings to translate into clinical applications.

Keywords: Gestational diabetes mellitus (GDM), fibrinogen-to-albumin ratio (FAR), inflammatory markers, insulin resistance, pregnancy complications

Öz

Amaç: Tüm gebeliklerin yaklaşık %15'i gestasyonel diabetes mellitus (GDM) ile sonuçlanabilmektedir. GDM enflamatuvar belirteçlerde ve insülin duyarlılığında önemli değişikliklerle ilişkili, yaygın bir metabolik hastalıktır. Gebelikte daha yüksek fibrinojen ve daha düşük albümin seviyeleri görülmektedir. Buna ek olarak GDM de enflamatuvar bir süreç olduğundan fibrinojen-albümin oranının (FAR) normal gebelere oranla daha fazla artabileceği, hastalığın şiddetinin göstergesi olarak potansiyel bir rol oynayabileceğini düşündürmektedir. Bu çalışmanın amacı, hamile kadınlarda GDM şiddeti ile FAR arasındaki bağlantıyı araştırmaktır.

Gereç ve Yöntem: Giresun Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi'nde prospektif gözlemsel bir çalışma yürütüldü. Çalışmaya GDM (n=41) ve kontrol (n=46) gruplarına ayrılan 87 gebe kadın dahil edildi. Demografik, klinik ve biyokimyasal parametrelere ilişkin veriler toplandı ve FAR hesaplandı. Grupları karşılaştırmak ve FAR'ninn tanısal performansını değerlendirmek için istatistiksel analizler yapıldı

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Bulgular: GDM grubunda kontrol grubuna kıyasla anlamlı olarak daha yüksek fibrinojen düzeyleri (440±73,8 mg/dL'ye karşılık 403±57,9 mg/dL, p=0,012) ve FAR (12,28'e karşılık 10,07, p<0,001) ve daha düşük albümin düzeyleri (36,61'e karşılık 38,80 g/L, p<0,001) vardı. FAR ile tahmini fetal ağırlık arasında pozitif yönde, zayıf derecede bir korelasyon bulundu (p=0,04, r=0,22). ROC analizi, FAR'nin 0,810 eğri altında kalan alan, %78 duyarlılık ve %71,7 özgüllük ile GDM için iyi bir tanısal doğruluğa sahip olduğunu gösterdi.

Sonuç: Bu çalışmada FAR, GDM olan gebelerde önemli ölçüde yükselmekte ve fetal büyüme ile korelasyon göstermektedir. Çalışmanın sonuçları, GDM yönetiminde yeni bir biyobelirteç olarak FAR'nin potansiyelini desteklemektedir. Ancak, bu bulguların klinik uygulamalara dönüşmesi için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus (GDM), fibrinojen-albümin oranı (FAR), enflamatuvar belirteçler, insülin direnci, gebelik komplikasyonları

Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance that is first recognized during pregnancy and is categorized into two types: A1GDM, controlled through diet, and A2GDM, which requires medication for glycemic control. During pregnancy, metabolic changes, particularly insulin action and sensitivity, increase owing to insulin resistance and hyperglycemia, peaking in the second half of pregnancy (1-3).

GDM management begins with non-pharmacological methods including dietary modifications, exercise, and glucose monitoring. The American Diabetes Association (ADA) recommends nutritional counseling and regular physical activity. Insulin therapy is introduced if glucose levels remain high despite lifestyle changes, with specific dosing strategies based on the trimester and blood glucose targets (2).

GDM is associated with increased levels of inflammatory markers, including pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), and reduced anti-inflammatory cytokines (IL-4 and IL-10). This inflammatory dysregulation is more pronounced in women with GDM than in those without non-GDM pregnancies (4-6).

The fibrinogen-to-albumin ratio (FAR) is a novel marker of inflammation and has been associated with various adverse outcomes, including myocardial infarction, stroke, and cancer. Fibrinogen levels increase during pregnancy, whereas albumin levels decrease because of the inflammatory response. Given that GDM is an inflammatory process, FAR could be higher in GDM patients than in non-GDM pregnancies, potentially serving as a marker of GDM severity. However, no studies have investigated whether FAR can predict disease progression in pregnant women with GDM (7-14).

This study aimed to investigate the relationship between the severity of GDM and FAR. This topic encompasses an important area in both clinical practice and the scientific literature. Identifying new biomarkers for the management of GDM and prevention of complications could provide valuable contributions to the field.

Materials and Methods

Study Design and Setting

Giresun Maternity and Children Training and Research Hospital served as the study site. Pregnant women receiving standard prenatal care at obstetrics and perinatology clinics constituted the study population. This study had a prospective observational design.

Women aged 18-40 years with GDM diagnosed by 75 g oral glucose tolerance test (OGTT) and women who were pregnant but not diagnosed with GDM were included in the study.

Women with several pregnancies were excluded from the study. Women who declined to participate in the research, women suffering from mental illnesses, and comorbidities included recurrent spontaneous abortions, immunological disorders, hematological disorders, chronic hypertension, chronic nephropathy, liver disease, heart disease and smoking.

Patients diagnosed with GDM were enrolled in the dietary group. However, patients with fasting blood glucose >95 mg/dL and postprandial blood glucose >140 in the 1st hour and >120 in the 2nd hour were included in the insulin treatment. The daily insulin dose was divided as follows: Half was administered as long-acting insulin (detemir) as basal insulin at bedtime, and the other half as rapid-acting insulin (aspart) before meals.

Sample Size

Using the G*Power program (version 3.1.9.4 Heinrich-Heine-Universitat, Düsseldorf, Germany) with similar publications in the literature, Cohen's d effect size was 0.80, alpha(α) value was 0.05, power (1-β) value was 0.80, and the minimum sample size required for statistical significance was 72, including 36 patients from the GDM group and 36 patients from the non- GDM (NGDM) group.

GDM Diagnostic Standards

A 75 g OGTT was used to diagnose GDM according to the ADA guidelines (OGTT). Following a minimum 8- hour overnight fast, plasma glucose levels were assessed at one and two hours

after glucose consumption (12). The diagnostic thresholds were as follows:

- Plasma glucose at fasting: ≥92 mg/dL (5.1 mmol/L);
- Plasma glucose after one hour: ≥180 mg/dL (10.0 mmol/L);
- Plasma glucose after two hours: ≥153 mg/dL (8.5 mmol/L).

Data Collection

Both Direct patient interviews and medical records were used to gather data. The subsequent variables were noted: Age, gender, body mass index, number of pregnancies, gestational age, consanguinity, number of stillbirths, presence of other disorders, and usage of medication are among the demographic and clinical variables.

The following parameters were measured in the laboratory: Levels of creatinine, calcium, albumin, glucose, platelets, white blood cells, neutrophils, and lymphocytes, and complete blood count. Individuals with GDM were treated with insulin as necessary in addition to dietary changes. The treatment plan was documented for all the patients.

Biochemical Analysis

Venous blood samples were collected in BD Vacutainer Sodium Citrate Tube (3.2%=0.109M) and centrifuged at 1500 x g for 15 min to obtain plasma samples. Plasma Fibrinogen levels (mg/dL) were measured based on the fibrinogen clotting time using the Clauss method by Diagon Coag XL (Diagon Ltd., Budapest, Hungary).

Venous blood samples were collected in a BD Vacutainer SST II Advance. It was centrifuged at 1500 x g for 10 min to obtain serum samples. Serum albumin levels (g/L) were measured using the Colorimetric Bromocresol Green method using Cobas c501 (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

IBM Corp., Armonk, New York, USA, SPSS version 26.0 was used for all statistical analyses. The normality of the data was evaluated using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Mean ± standard deviation was used to report normally distributed (parametric) data, whereas the median (25^{th}-75^{th} percentile) was used to report non-normally distributed (non-parametric) data. To compare demographic, biochemical, and clinical data between the GDM and control groups, the Mann-Whitney U test was used for non-parametric variables and Student's t-test for parametric variables. GDM subgroups were compared based on treatment modality using the same assays. The associations between FAR and biochemical and demographic factors were assessed using the Spearman's correlation test. The diagnostic sensitivity, specificity, accuracy, and area under the curve (AUC) of the tests were assessed using receiver operating characteristic (ROC) analysis. The Youden index was used to establish a proper cut-off value. Statistical significance was attained when the p-value was less than 0.05.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Giresun Training and Research Hospital Local Ethics Committee granted clearance (decision no.: 03.04.2024/07, date: 05.04.2024). Before inclusion in the study, each participant provided informed consent.

Results

The participants consisted of 41 GDM pregnancies and 46 controls. Biochemical results and clinical and demographic data are presented in Table 1. The average age There were no statistically significant differences between the GDM and control groups regarding gravidity, parity, estimated fetal weight (EFW), or gestational week at blood sampling (p>0.05).

The fibrinogen and FAR levels were significantly higher in the GDM group than in the control group (p<0.05). Albumin levels were significantly lower in the GDM group (p<0.05) (Table 1).

Pregnancies with GDM were divided into two groups according to the treatment method: those treated with insulin

Table 1: Comparing demographic, biochemical and clinical data of the GDM between control group

	GDM (n=41)	Control (n=46)	p-value*
Age (year)	30.93±4.76	31.07±5.47	0.910
Gravidity	2.15±1.15	2.12±1.12	0.448
Parity	0.92±0.87	0.73±0.97	0.185
Gestational week	31 (29-33)	29 (26-32)	0.06
EFW (gram)	1766±914	1521±761	0.069
Fibrinogen (mg/dL)	440±73.8	403±57.9	**0.012**[a]
Albumin (g/L)	36.31 (33.75-37.77)	38.80 (36.97-40.35)	**<0.001**[b]
FAR	12.28 (10.74-13.69)	10.07 (9.33-11.01)	**<0.001**[b]

*: p=0.05 statistical significance. Paremetric data are presented mean ± standard deviation. [a]: Student's t-test was utilised. Non-parametric data are presented median (25^{th}-75^{th} percentile), [b]: Mann-Whitney U test was utilised, GDM: Gestational diabetes mellitus, EFW: Estimated fetal weight, FAR: Fibrinogen albumin ratio

Table 2: Comparison of demographic, biochemical and clinical data of the GDM group according to treatment method			
	Diet (n=20)	**Insulin (n=21)**	**p-value***
Age (year)	31.11±5.19	30.78±7.22	0.832
Gravidity	2.13±1.07	2.16±1.18	0.418
Parity	0.97±0.86	0.85±0.79	0.217
Gestational week	33.5 (29 -35)	31 (27.5-32.5)	0.236
EFW (gram)	1687±650	1821±713	0.148
Fibrinogen (mg/dL)	441.4±76.31	438.7±73.22	0.548[a]
Albumin (g/L)	36.70 (33.32-37.60)	36.58 (33.95-38.10)	0.296[b]
FARs	11.99 (10.78-13.31)	12.37 (10.63-13.88)	0.639[b]

*: p=0.05 statistical significance. Parametric data are presented mean ± standard deviation, [a]: Student's t-test was utilised. Non-parametric data are presented median (25th-75th percentile), [b]: Mann-Whitney U test was utilised, EFW: Estimated fetal weight, FAR: Fibrinogen albumin ratio

Table 3: Correlations between FAR and demographic, biochemical parameters		
In all groups (n=87)	**Correlation coefficient (r)**	**p-value**
Age (year)	-0.110	0.308
Gravidity	-0.073	0.399
Parity	-0.010	0.924
Gestational week	0.197	0.066
EFW **(gram)**	0.220	**0.040***

*: Spearman Correlation analysis was utilized, FAR: Fibrinogen albumin ratio, EFW: Estimated fetal weight

Table 4: Receiver operating curve analysis of biochemical marker						
Parameter	**AUC**	**95% CI**	**Cut-off value**	**Sensitivity**	**Specificity**	**p-value**
Fibrinogen (mg/dL)	0.659	0.544-0.774	>434	53.7%	76.1%	<0.001
Albumin (g/L)	0.767	0.669-0.865	>37.25	69.6%	65.9%	<0.001
FAR	**0.810**	0.718-0.903	**>10.69**	**78%**	**71.7%**	<0.001

AUC: Area under curve, CI: Confidence interval, FAR: Fibrinogen albumin ratio

(n=21) and those treated with diet (n=20). The two subgroups were analyzed. However, the Mann-Whitney U test and Student's t-test showed that gravidity, parity, EFW, gestational week at blood sampling, fibrinogen, albumin, and FAR between the different treatment methods were not statistically significant (p>0.05) (Table 2).

The correlations between FAR levels and biochemical and demographic variables are shown in Table 3. The FAR levels were positively and weakly correlated with EFW (p=0.04, r=0.22). No significant correlations were found between FAR levels and age, gravidity, parity, or gestational week at blood sampling.

According to the ROC analysis, FAR had the highest AUC value compared to fibrinogen and albumin at 0.810, 0.659, and 0.767, respectively (p<0.001) (Figure 1, Table 4). According to ROC analysis and Youden index FAR level was 10.69 to differentiate GDM pregnancies from controls with 78% sensitivity and 71.7% specificity [95% confidence interval= (0.718-0.903), p<0.001].

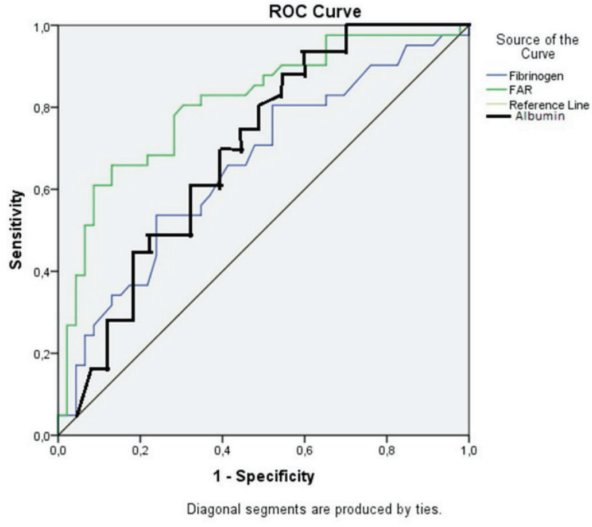

Figure 1: ROC analysis
ROC: Receiver operating characteristic

Discussion

This study aimed to investigate the relationship between the severity of GDM and FAR. Compared to the control group, the GDM group had significantly higher fibrinogen levels (440±73.8 mg/dL vs. 403±57.9 mg/dL, p=0.012), lower albumin levels (36.61 vs. 38.80 g/L, p<0.001), and a higher FAR (12.28 vs. 10.07, p<0.001). A weak positive correlation was found between EFW and FAR (p=0.04, r=0.22). ROC analysis demonstrated that FAR had an AUC of 0.810, a sensitivity of 78%, and a specificity of 71.7%, indicating acceptable diagnostic accuracy for GDM.

The FAR levels were positively and weakly correlated with EFW. This is particularly important, as GDM is associated with an increased risk of macrosomia and related complications.

Interestingly, no significant differences were found in FAR, fibrinogen, or albumin levels between GDM patients treated with insulin and those managed with a diet alone. This may be because glycemic control is achieved with diet or insulin, and FAR is related to glycemic control. In our study, glycemic control was achieved using both diet and insulin. To explain this situation, studies in which an uncontrolled blood glucose group was also included are required.

Previous studies have identified inflammation as a key determinant in the development of GDM. Kansu-Celik et al. (16) reported that high CRP levels in the first trimester are risk factors for the later development of GDM during pregnancy. Ureyen Ozdemir et al. (17) studied the C-reactive protein/albumin ratio (CAR), a recently emerging marker of inflammation, in patients with GDM. Their findings indicated that CAR levels in pregnant women with GDM were significantly higher compared to those in healthy pregnant women (17).

Yilmaz et al. (18) investigated the relationship between the neutrophil-lymphocyte ratio (NLR), another inflammatory marker, and GDM. They concluded that inflammation plays a central role in the pathogenesis of GDM and that NLR is a reliable marker for the disease (18).

Previous studies have linked inflammation to insulin resistance. Elevated levels of advanced glycation end-products in circulation are associated with inflammation and GDM, suggesting that this may play a key role in the underlying pathology of GDM (18).

Fibrinogen is mostly produced by the liver and is a good indicator of coagulation status and inflammation, especially after vascular injury. In the presence of tissue injury and an inflammatory response, its concentration rises dramatically (20-22), linked to microvascular issues in patients with type 2 diabetes (23). In addition, albumin plays a crucial role in extracellular antioxidant activity and immune defense, shows protective anti-inflammatory effects, and is linked to microvascular complications in type 2 diabetes mellitus. The FAR has been found to more accurately reflect inflammation than fibrinogen or albumin alone (24).

Generally, during pregnancy, a series of physiological changes occur in the human hemostatic system as hormones change rapidly, including elevation of coagulation factors, reduction of anticoagulant substances, and decrease in fibrinolytic activity, which finally results in the formation of a hypercoagulable state (25,26). Compared to women who are not pregnant, fibrinogen levels rise sharply in the first trimester of pregnancy and remain elevated in the third trimester (13,27).

Underlying mechanism of FAR increase in GDM patient; fibrinogens also play a role in the development of insulin resistance and impaired glucose control. In contrast, low albumin levels worsen inflammation by increasing the synthesis of molecules that bind cells to one another and reducing the elimination of free radicals (8). The production of hepatic fibrinogen may be stimulated by elevated free fatty acid release during the pathophysiology of insulin resistance and type II diabetes. Visceral fat quantity is strongly correlated with high plasminogen activator inhibitor-1 levels, indicating that insulin resistance syndrome, which predates type II diabetes, may have a greater influence than diabetes itself (8,24). TNF-α is known to increase the synthesis of hepatic fibrinogen and has been implicated in the insulin resistance observed in human obesity, according to recent investigations. Thus, hyperfibrinogenemia may result from specific pathogenic conditions linked to the insulin resistance syndrome (8).

FAR in pregnant women has been studied in conditions such as preeclampsia (28), recurrent pregnancy loss (29), early pregnancy loss (30), and venous thrombosis (31) with FAR found to be elevated FAR. In a study by Ren et al. (28), it was found that the FAR increased in proportion to the severity of preeclampsia, with higher FAR observed in severe preeclampsia compared to mild preeclampsia and the control group.

However, FAR has not yet been studied in pregnant women with diabetes. To the best of our knowledge, this is the first study to investigate FAR in GDM.

Our results align with those of previous research indicating elevated fibrinogen levels in GDM patients. Fibrinogen, an acute-phase reactant, increases in response to inflammation and tissue injury, which are common in GDM. Compared to healthy pregnant women, women with GDM have a greater incidence of thrombophilia, which has been linked to elevated fibrinogen levels.

Study Limitations

This study has several limitations. Conducted at a single center with a small sample size, the generalizability of the results may be constrained. In addition, the cross- sectional

design limits the ability to establish causality. Future research should involve larger, multicenter cohorts, employ longitudinal designs to validate these findings, and further investigate the potential of FAR as a prognostic marker for complications associated with GDM.

Conclusion

The study concluded that pregnant patients with GDM have a significantly higher FAR. These findings support the potential of FAR as a novel biomarker for GDM management. However, further research is required to translate these results into clinical applications.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. The Giresun Training and Research Hospital Local Ethics Committee granted clearance (decision no.: 03.04.2024/07, date: 05.04.2024).

Informed Consent: Before inclusion in the study, each participant provided informed consent.

Footnoes

Authorship Contributions

Surgical and Medical Practies: M.A., Concept: M.A., Design: M.A., Data Collection and Processing: M.A., H.F.A., Analysis or Interpretation: M.A., H.F.A., Literature Search:M.A., H.F.A., Writing: M.A.

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Comparison of FOLFOX/CAPOX and Sorafenib in Locally Advanced or Metastatic Hepatocellular Carcinoma

Lokal İleri veya Metastatik Hepatoselüler Karsinomda FOLFOX/CAPOX ve Sorafenib Karşılaştırması

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Abstract

Objectives: Liver cancer ranks third in terms of mortality worldwide. Sorafenib is a tyrosine kinase inhibitor that was approved for patients with advanced hepatocellular cancer (HCC). There are not many large-scale studies comparing sorafenib with chemotherapy. We planned to compare the effectiveness of sorafenib and chemotherapy in advanced-stage HCC patients.

Materials and Methods: Patients over the age of 18, who were followed up with a diagnosis of advanced stage HCC in the Medical Oncology Department at Ankara University Faculty of Medicine between 2012 and 2022, who received sorafenib or FOLFOX/CAPOX treatment as first-line treatment, were included in the study. Patient and disease characteristics were recorded from the hospital database (Avicenna) and compared statistically.

Results: Forty-four patients were included. The Eastern Cooperative Oncology Group performance status of all patients was 0-1. Nine (22.5%) patients had liver cirrhosis. The distribution of Child-Pugh scores was similar between groups (p=0.45). It was seen that 22 (50%) patients had stage A-B disease and 22 (50%) patients had stage C disease. It was recorded that 37 (84.1%) patients received sorafenib and 7 (15.9%) patients received FOLFOX/CAPOX treatment. Progression-free survival was measured as 2 months for the FOLFOX/CAPOX arm and 1 month for the sorafenib arm (p=0.96, log-rank). Overall survival was measured as 8.8 months in the FOLFOX/CAPOX arm and 6.3 months in the sorafenib arm (p=0.29, log-rank).

Conclusion: No difference in survival was demonstrated between sorafenib and FOLFOX/CAPOX treatment. Multicenter and larger population studies are needed to elucidate the place of fluoropyrimidine and oxaliplatin combination in HCC treatment.

Keywords: Hepatocellular carcinoma, liver cancer, chemotherapy, sorafenib

Öz

Amaç: Karaciğer kanseri, akciğer ve kolorektal kanserden sonra dünya çapında mortalite açısından üçüncü sırada yer almaktadır. Sorafenib, 2007 yılında inoperabl hepatoselüler kanser (HCC) hastalarında onay almış bir tirozin kinaz inhibitörüdür. Sorafenibin kemoterapi ile kıyaslandığı geniş çaplı fazla sayıda çalışma olmadığı görülmektedir. Bu çalışmada ileri evre HCC hastalarında sorafenib ile kemoterapi etkinliğinin karşılaştırılması planlandı.

Gereç ve Yöntem: Ankara Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji bölümünde 2012-2022 arasında ileri evre HCC tanısı ile takip edilen, birinci basamak tedavide sorafenib veya FOLFOX/CAPOX tedavisi alan, 18 yaş üzerindeki hastalar çalışmaya dahil edildi. Hasta ve hastalık özellikleri hastane veritabanından (Avicenna) kaydedildi ve istatistiki olarak karşılaştırıldı.

Bulgular: Çalışmaya 44 hasta dahil edildi. Tüm hastaların Doğu Kooperatif Onkoloji Grubu performans durumu 0-1 idi. Dokuz (%22,5) hastada karaciğer sirozu mevcuttu. Tümör evreleri değerlendirildiğinde 22 (%50) hastada evre A-B, 22 (%50) hastada evre C hastalık olduğu görüldü. Sistemik tedavilerde 37 (%84,1) hastanın sorafenib, 7 (%15,9) hastanın FOLFOX/CAPOX tedavisi aldığı kaydedildi. Child-Pugh skorlarının dağılımı gruplar arasında benzerdi (p=0,45). Progresyonsuz sağkalım FOLFOX/CAPOX kolu için 2 ay, sorafenib kolu için 1 ay olarak ölçüldü (p=0,96, log-rank). Genel sağkalım FOLFOX/CAPOX kolunda 8,8 ay, sorafenib kolunda ise 6,3 ay olarak ölçüldü (p=0,29, log-rank).

Sonuç: Sorafenib ile FOLFOX/CAPOX tedavisi arasında sağkalım açısından fark gösterilemedi. Fluoropirimidin ve okzaliplatin kombinasyonunun HCC tedavisindeki yerinin aydınlatılması için çok merkezli ve daha geniş popülasyonlu çalışmalara gereksinim vardır.

Anahtar Kelimeler: Hepatoselüler karsinom, karaciğer kanseri, kemoterapi, sorafenib

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Introduction

Liver cancer ranks third in terms of mortality worldwide, after lung and colorectal cancer (1). Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, with a rate of around 80% (2). New treatment options for this disease, which has a very high mortality rate, especially in the advanced stages, are an important research topic in the oncology literature.

The Barcelona Clinic Liver Cancer (BCLC) system, which is widely accepted for staging and treatment selection, integrates the Child-Pugh score, which is used as the gold standard in determining liver functional reserve, apart from the extent of the disease (3,4). This system is widely used in HCC treatment decision. Among the new systemic treatments for advanced stage patients who are not suitable for local treatments, the combination of atezolizumab and bevacizumab, which has been shown to be superior to sorafenib, and the combination of durvalumab and tremelimumab, stand out (5,6). However, it is not possible to use these agents in many patients due to reasons such as availability of the drugs and reimbursement conditions.

Sorafenib is a tyrosine kinase inhibitor (TKI) approved in 2007 for inoperable HCC patients and is now widely used in advanced-stage disease. Sorafenib was compared with placebo in its study in advanced disease, with median survivals reported as 10.7 and 7.9 months, respectively (7). Although it is known that the effectiveness of chemotherapy is limited, especially in patients with chronic liver disease-related complications and high volume disease (8), after the approval of sorafenib, it appears that there are not many large-scale studies comparing sorafenib with chemotherapy. A recently published study has shown that hepatic artery infusion of fluorouracil (5-FU) and oxaliplatin (OXA) may be superior to sorafenib in disease limited to the liver (9).

In this study, we planned to compare the effectiveness of sorafenib and chemotherapy in advanced-stage HCC patients.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and Regulations in drug research Ministry of Health, Goverment of Türkiye, January 29,1993. Ankara University Faculty of Medicine Ethics committee approved the study protocol (decision no.: İ03-280-24, date:24.04.2024). All patients signed informed consent to participate in retrospective studies before initial presentation.

Patients over the age of 18, who were diagnosed with advanced stage HCC and were treated with sorafenib or FOLFOX/CAPOX in first-line treatment, at Ankara University Faculty of Medicine, Medical Oncology Department between 2012 and 2022, were included in the study. Previous trans-arterial chemo-embolization treatment was not considered an exclusion criteria. Patients who did not receive sorafenib or FOLFOX/CAPOX chemotherapy in first-line treatment, who had a local treatment option and whose data were not available were excluded. Information such as age, comorbidities, HCC etiology, BCLC stage, previous local treatments, Child-Pugh score, encephalopathy and ascites status were recorded from the hospital database (Avicenna).

Statistical Analysis

Statistical analysis was performed with R version 4.1 (R foundation) program. The distribution of variables was evaluated visually (histogram and probability plots) and analytically (Kolmogorov-Smirnov/Shapiro-Wilk tests, according to number of patients). Descriptive statistics were given as mean and standard deviation for normally distributed variables. Chi-Square test was used to compare categorical variables. Kaplan-Meier analysis and log-rank test were used for survival tests, including analysis for progression free and overall survival for FOLFOX/CAPOX and sorafenib treatments. For statistical significance, type-1 error level was accepted as 5%.

Results

Forty-four patients were included in the study. Forty patients (91%) were male and 4 patients (9%) were female. The Eastern Cooperative Oncology Group performance status of all patients was 0-1. When comorbidities were evaluated, 14 (31.8%) patients had hypertension, 15 (34.1%) patients had diabetes mellitus, and 7 (15.9%) patients had atherosclerotic cardiovascular disease. Nine (22.5%) patients had liver cirrhosis. When the Barcelona stages of the tumor were evaluated, it was seen that 22 (50%) patients had stage A-B disease and 22 (50%) patients had stage C disease. When the etiology was examined, it was seen that 21 (47.7%) patients had hepatitis B and 4 (9.1%) patients had hepatitis C. Thirty-two (72.7%) patients received local treatment before systemic treatment. In systemic treatments, 37 (84.1%) patients received sorafenib and 7 (15.9%) patients received FOLFOX/CAPOX treatment. The clinical characteristics of the patients are summarized in Table 1.

It was observed that 22 (59.4%) of 37 patients receiving sorafenib were Child-Pugh category A, and 15 (40.5%) were B. It was noted that in the FOLFOX/CAPOX group, 3 (42.9%) patients were category A and 4 (57.1) patients were category B. There were no Child-Pugh C patients. The distribution of Child-Pugh scores was similar between groups (p=0.45). While ascites was not observed in 27 (72.9%) patients in the sorafenib group, ascites was slight in 9 (24.3%) patients and moderate in 1 (2.7%) patient. In the FOLFOX/CAPOX group, 2 (28.6%) patients had slight ascites. There was no difference between the groups in terms of ascites. Hepatic encephalopathy was not observed in any patient (Table 2).

Table 1. Patient characteristics				
	Male (n=40)	**Female (n=4)**	**Total (n=44)**	**p-value**
Age, mean (+/- SD)	65.5 (9.22)	59.3 (18.2)	64.9 (10.2)	0.25
ECOG performance status 0-1, n (%)	40 (100%)	4 (100%)	44 (100%)	
Comorbidities, n (%)				
Hypertension	12 (30%)	2 (50%)	14 (31.8%)	0.41
Diabetes mellitus	13 (32.5%)	2 (50%)	15 (34.1%)	0.48
Atherosclerotic cardiovascular disease	7 (17.5%)	-	7 (15.9%)	0.36
Cirrhosis	9 (22.5%)	-	9 (20.5%)	0.29
Stage (Barcelona)				
A-B	21 (42.5%)	1 (25%)	22 (50%)	0.50
C	19 (47.5%)	3 (75%)	22 (50%)	
HCC etiology				
Hepatitis B	19 (47.5%)	2 (50%)	21 (47.7%)	0.74
Hepatitis C	3 (7.5%)	1 (25%)	4 (9.1%)	
Other/unknown	18 (45%)	1 (25%)	19 (43.2%)	
Local treatment	30 (75%)	2 (50%)	32 (72.7%)	0.28
Systemic treatment				
Sorafenib	34 (85%)	3 (75%)	37 (84.1%)	0.60
FOLFOX/CAPOX	6 (15%)	1 (25%)	7 (15.9%)	
SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group				

Table 2. Distribution of patients according to Child-Pugh scores and ascites status				
	Sorafenib (n=37)	**FOLFOX/CAPOX (n=7)**	**Total (n=44)**	**p-value**
Child-Pugh				
A	22 (59.4%)	3 (42.9%)	25 (56.8%)	0.45
B	15 (40.5%)	4 (57.1%)	19 (43.2%)	
Ascites				
Absent	27 (72.9%)	5 (71.4%)	32 (72.7%)	0.89
Slight	9 (24.3%)	2 (28.6%)	11 (25%)	
Moderate	1 (2.7%)	-	1 (2.2%)	
No encephalopathy	37 (100%)	7 (100%)	44 (100%)	

Progression-free survival was measured as 2 months for the FOLFOX/CAPOX arm and 1 month for the sorafenib arm (p=0.96, log-rank, Figure 1).

Overall survival was measured as 8.8 months in the FOLFOX/CAPOX arm and 6.3 months in the sorafenib arm (p=0.29, log-rank, Figure 2).

Discussion

The results of our study show that there is no difference in overall and progression-free survival between FOLFOX/CAPOX and sorafenib. Although our study has limitations such as a small and heterogeneous patient population, possible data loss due to retrospective design, and being a single-center study, it contributes to the literature since there are very few studies comparing chemotherapy with sorafenib in the treatment of HCC.

It is known that chemotherapy has limited effectiveness in the treatment of HCC and optimal chemotherapy regimen is unknown. Although response rates are low, there is evidence in the literature that these rates are affected by factors such as tumor burden, performance status, tumor thrombus and bilirubin level (8).

Sorafenib is a TKI approved in 2007 for inoperable HCC patients and is now widely used in advanced stage disease (7). It is known that for this disease, where mortality is quite high and treatment options are limited, the number of agents that demonstrate a survival advantage is quite low. Although the median survival with sorafenib was reported as 10.7 months in

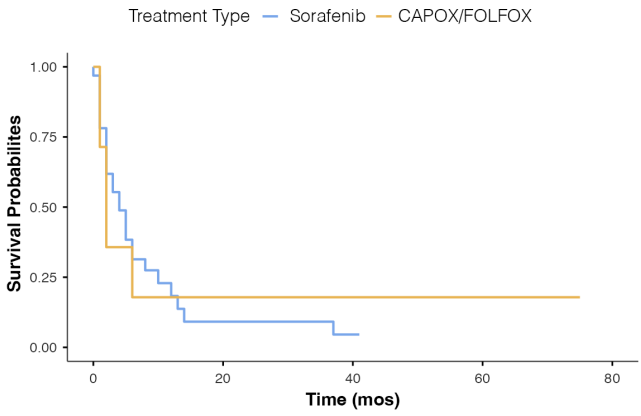

Figure 1: Progression-free survival in patients receiving FOLFOX/CAPOX and sorafenib

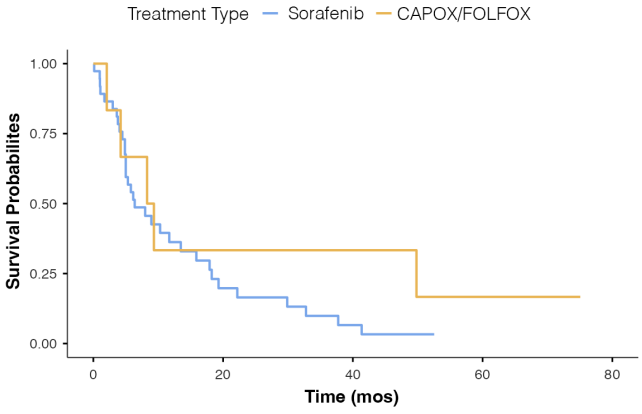

Figure 2: Overall survival in patients receiving FOLFOX/CAPOX and sorafenib

the SHARP trial, a point that should be noted in this study is that the drug was compared with placebo. Although there are trials for immunotherapy and other tyrosine kinase inhibitors in the literature (10,11), there do not seem to be many studies comparing chemotherapy with sorafenib. In a phase 3 trial, which included 356 patients, comparing sorafenib alone and the sorafenib-doxorubicin combination, no significant difference on survival could be demonstrated (12). In another phase 2 trial which included 94 patients, sorafenib alone and the gemcitabine-OXA-sorafenib combination were compared. Although a better objective response rate was achieved in the chemotherapy arm, no significant progression-free survival advantage was demonstrated (13). It appears that sorafenib has not been compared head-to-head with chemotherapy in large-scale studies. In addition, availability of immunotherapy and other combination treatments, which have been shown to be superior in first-line treatment in advanced disease, is limited, and there appears to be an unmet need in advanced disease.

In our study, no superiority of sorafenib over FOLFOX/CAPOX chemotherapy was observed in first-line treatment of HCC patients who were not suitable for local treatment options. In addition, overall survival was observed to be longer in patients who responded to FOLFOX/CAPOX treatment, despite not reaching statistical significance, probably due to low patient count. In a recent phase 3 trial including 262 patients, hepatic arterial infusion of 5-FU/OXA treatment was compared with sorafenib, and overall survival was reported as 13.9 and 8.2 months, respectively (9). An important point in this study is that local treatments could be applied to 16 patients after treatment, and the median survival in this group was reported as 20.8 months, while survival in high-risk patients was reported as 5.7 months versus 10.8 months. In another phase 3 trial comparing sorafenib alone with the combination of hepatic arterial infusion chemotherapy in patients with portal vein tumor thrombosis, a sign of high risk and poor prognosis, survivals were reported as 16.3 and 6.5 months, respectively (14). However, it was also reported in this study that the toxicity of combination therapy was higher. These studies suggest that 5-FU and OXA chemotherapy regimens may be effective in the treatment of HCC and are consistent with the findings of our study. These findings suggest that 5-FU and OXA chemotherapy may provide a survival advantage in some patient subgroups. Since our study included a small number of patients, it was not possible to assess the subgroups in which chemotherapy could be most beneficial. Identification of these patient subgroups and factors that may indicate chemotherapy sensitivity is crucial, especially for a patient population that has limited access to new combination therapies that have been shown to be superior to sorafenib, and may guide individualization of treatment and provide a survival advantage in this patient group.

In conclusion, no difference in survival was demonstrated between sorafenib and FOLFOX/CAPOX treatment in our study. Multicenter and larger population studies are needed to elucidate the place of fluoropyrimidine and OXA combination in HCC treatment.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and Regulations in drug research Ministry of Health, Goverment of Türkiye, January 29,1993. Ankara University Faculty of Medicine Ethics committee approved the study protocol (decision no.: İ03-280-24, date:24.04.2024).

Informed Consent: All patients signed informed consent to participate in retrospective studies before initial presentation.

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Footnotes

Authorship Contributions

Concept: M.Y., E.C.E., E.B.K., Design: M.Y., E.B.K., Data Collection and/or Processing: M.Y., B.B.K., H.B., Analysis and/or Interpretation: E.C.E., Literature Search: E.C.E., B.B.K., H.B., Writing: M.Y., E.B.K.

Conflict of Interest: There is no potential conflict of interest to declare.

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Mediating Effect of Caudate Nucleus Dopaminergic Activity on the Relationship Between Age and Cognitive Functions in Parkinson's Disease Patients

Parkinson Hastalarında Kaudat Çekirdek Dopaminerjik Aktivitesinin Yaş ve Bilişsel İşlevler Arasındaki İlişkiye Aracılık Etkisi

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Abstract

Objectives: Advancing age is the primary risk factor for Parkinson's disease (PD). In PD patients, dopaminergic activity is impaired, and cognitive dysfunctions are observed. This study investigated the mediating effect of caudate nucleus dopamine transporter binding score on the relationship between age and cognition in PD patients.

Materials and Methods: The open database of the Michael J. Fox Association was used, and data on 1,099 PD patients were accessed. Cognitive function scores and single-photon emission tomography findings assessing caudate nucleus dopaminergic activity were used.

Results: The caudate nucleus dopamine transporter binding score mediated the relationship between age and attention, processing speed, linguistic function, working memory, verbal episodic memory, and visual-spatial functions.

Conclusion: The cumulative neurodegenerative effect of age and PD requires monitoring of cognitive function. This study emphasizes the significance of considering dopaminergic activity in the caudate nucleus for diagnosing, monitoring, and treating cognitive functions in Parkinson's disease.

Keywords: Parkinson's disease, mediation analysis, cognition, caudate nucleus, dopamine transporter

Öz

Amaç: İlerleyen yaş, Parkinson hastalığı için birincil risk faktörüdür. Parkinson hastalarında, dopaminerjik aktivite bozulur ve bilişsel işlev bozuklukları görülür. Bu çalışmanın amacı, Parkinson hastalarında yaş ve biliş ilişkisinde, kaudat çekirdek dopamin taşıyıcısı bağlanma skorunun aracılık etkisinin araştırılmasıdır.

Gereç ve Yöntem: Michael J. Fox Derneğinin erişime açık veritabanı kullanılmış, 1.099 Parkinson hastasının verilerine erişim sağlanmıştır. Hastaların bilişsel işlev puanları ve kaudat çekirdek dopaminerjik aktivitesini değerlendiren tek foton emisyon tomografisi bulguları kullanılmıştır.

Bulgular: Kaudat çekirdek dopamin taşıyıcısı bağlanma skoru, yaş ile dikkat, işlem hızı, dilsel işlev, çalışma belleği, sözel epizodik bellek ve görsel-uzamsal işlevler arasındaki ilişkiye aracılık etmiştir.

Sonuç: Yaş ve Parkinson hastalığının kümülatif nörodejeneratif etkisi, bilişsel işlevlerin takibini gerektirmektedir. Bu çalışma, Parkinson hastalığında bilişsel işlevlerin tanı, takip ve tedavisinde, kaudat çekirdek dopaminerjik aktivitesinin dikkate alınmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Parkinson hastalığı, aracılık analizi, biliş, kaudat çekirdek, dopamin taşıyıcısı

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, affecting more than 6 million people worldwide (1). In addition to motor symptoms, including bradykinesia, rigidity, tremors, and postural instability, non-motor symptoms, including cognitive dysfunctions, pain, fatigue, and autonomic disorders, accompany the course of the disease and worsen the prognosis (2).

The aging process and neurodegeneration are associated, with advanced age being the primary risk factor for PD (3). Several molecular features of aging, including oxidative damage and mitochondrial dysfunction, loss of protein homeostasis, neuroinflammation, genomic instability, and impaired stress responses, overlap with mechanisms involved in PD neurodegeneration (4). Studies have suggested that dopaminergic neurons are more sensitive to age-related loss of mitochondrial function and more vulnerable to resulting bioenergetic stress (5). The Rotterdam study, one of the early and comprehensive studies on the relationship between age and PD, was conducted with approximately 7,000 individuals over 55 years of age. It reported that the prevalence of PD was 0.3%, 1%, 3.1%, and 4.3% in the 55-64, 65-74, 75-84, and 85-94 age ranges, respectively (6). Many subsequent studies have consistently confirmed the association between aging and the development of PD (7-9).

It has been documented that non-motor symptoms were present in patients with an advanced age of onset at the time of PD diagnosis, and many patients had previously sought medical advice for these symptoms (10). Due to its combined impact on dopaminergic and non-dopaminergic pathways, advanced age may lead to a more prevalent and severe course of PD-related functional disorders. Indeed, it has been reported that older individuals with PD exhibit more extensive involvement of extra-striatal and non-dopaminergic systems compared to younger ones (11). Since non-motor symptoms are resistant to levodopa treatment, it has been suggested that PD-related disability is broadly related to these symptoms (12). Cognitive impairments, which are considered non-motor symptoms, develop six times more frequently in patients with PD than in the healthy population (13). A longitudinal study showed that approximately half of PD patients with normal cognition developed cognitive impairment within six years of their initial visit (14). Frequent cognitive complaints include impairments in attention, executive functions, visual-spatial skills, language, and memory functions (15,16). Cognitive decline may occur before or at the time of diagnosis of PD, as well as many years after the diagnosis, and shows high variability in terms of clinical severity, related cognitive domains, and rate of progression (16). However, age itself is the greatest risk factor for the development of dementia in PD (11).

The striatum, comprising the caudate nucleus and putamen, is a key component of the basal ganglia. In PD, the loss of dopaminergic neurons in the striatum leads to dysfunction and structural changes in basal ganglia-thalamocortical circuits, which are modulated by dopamine (17). The caudate nucleus is linked to the dorsolateral prefrontal cortex and lateral orbitofrontal cortex. Dopaminergic input to the caudate nucleus has been linked to brain circuit activity associated with cognitive functioning in early PD (18). Indeed, several studies have associated cognitive deficits in PD with dopaminergic dysfunction in the caudate nucleus (18-21). For instance, dopamine depletion in the caudate nucleus has been suggested to lead to early impairment of executive functions in PD, as evidenced by changes in dorsolateral prefrontal and anterior cingulate metabolism (19). Furthermore, individuals diagnosed with PD and cognitive impairment exhibited reduced presynaptic dopamine binding in the right caudate in comparison to those without cognitive impairment (20). Relatedly, impaired dopaminergic function of the caudate nucleus has been associated with impaired memory functions (21). Moreover, the dorsal caudate nucleus is a major target of the nigrostriatal pathway, and abnormal modulation in nigrostriatal dopaminergic circuits has also been connected to cognitive impairments in the early stages of PD (22,23). In this context, the shrinkage of the caudate nucleus with age, along with the reduction of both dopamine receptors and transporters (24,25), may further exacerbate the negative effects of PD on cognitive functions.

One important element of the dopaminergic system is the dopamine transporter (DAT), a protein located in the presynaptic terminal of dopaminergic neurons responsible for dopamine reuptake (26). The DAT is crucial in controlling synaptic dopamine levels, making it a key regulator of dopaminergic neuron connectivity. The DAT single-photon emission computed tomography (DAT-SPECT) is a new imaging technique used to assess the activity of dopamine in the striatum of the brain in individuals with PD. The DAT scan involves the injection of Ioflupane I-123 to visualize dopamine transporters in the striatum (27). The amount of Ioflupane I-123 binding to dopamine transporters indicates the levels of bound striatal DAT and, consequently, the dopamine levels in the striatum. The DAT scan has a high sensitivity (84.4%) and specificity (96.2%) and is used for differential diagnosis (28). The degree of striatal dopaminergic deficiency, measured by striatal binding ratios, is associated with the severity of motor symptoms of PD, overall disease severity, and some non-motor symptoms (29,30). Early dysfunction of caudate dopaminergic activity is also reported to be a predictor for future cognitive impairment (31-33).

Cognitive decline in individuals with PD leads to a lower quality of life and increased burden for both the patients and their caregivers (34). Thus, identifying the reasons behind this decline in cognitive functions may help develop new strategies for managing the disease. This study aims to investigate whether the level of dopaminergic activity in the caudate nucleus mediates the relationship between age and cognitive functions in early-stage PD patients.

Materials and Methods

The data for this study was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (35). PPMI is an international multicentric cohort study and it has been collecting data from newly diagnosed PD patients, people at risk, and unaffected controls since 2010. The study is based on a longitudinal design, with assessments taken at regular intervals. The findings in this study are based on the patients' initial assessment. Patients included in the study were over 30 years old and had not yet started medication such as levodopa, MAO-B inhibitors, dopamine agonists, and/or amantadine. The dataset was acquired from the PPMI website on 1.7.2024, and it only included data from PD patients. We accessed demographic data, caudate nucleus dopamine transporter binding score information, and cognitive test results of 1099 PD patients in the database. The PPMI protocol was reviewed and approved by the Institutional Review Board and the Independent Ethics Committee (IRB/IEC) at each center and the study followed the Guideline for Good Clinical Practice. Each participant provided written informed consent before being included in the study. This study obtained the right to use the PPMI database data.

Assessments

The cognitive functions were assessed using the following tests: Trail Making Test-A (TMT-A) (attention, executive functions), Digit Symbol Substitution Test (DSST) (processing speed), Montreal Cognitive Assessment (MoCA) (general cognition), Semantic Fluency Test (SFT) (linguistic function), Number Letter Sequencing Test (NLST) (executive function-working memory), Hopkins Verbal Learning Test (HVLT) (verbal episodic memory), and Line Orientation Test (LOT) (visual-spatial skills). TMT-A measured the time to complete the test, where a longer completion time indicates worse cognitive performance. All other cognitive tests measured accuracy scores, where a higher score indicates better cognitive performance.

DAT-SPECT analysis was conducted using Ioflupane I-123 to target the dopamine transporter during the scan as per the imaging technical manual (www.ppmi-info.org). The scans were performed at various imaging centers and then sent to the PPMI imaging central laboratory at the Neurodegenerative Disorders Institute in New Haven, where two expert readers visually interpreted the results. To ensure consistency of the reconstructions for all imaging centers, the SPECT raw data was reconstructed using HERMES (Hermes Medical Solutions, Skeppsbron 44, 111 30 Stockholm, Sweden) and then processed in PMOD (PMOD Technologies, Zurich, Switzerland). Attenuation correction and filtering (a standard Gaussian 3D 6.0 mm) were applied, and the images were normalized to a standard anatomical alignment. Next, the highest striatal uptake slice was identified, and the eight hottest striatal slices around it were averaged. Regions of interest were placed on the left and right caudate, and the count densities were extracted for each striatal region, and the specific binding ratio for the caudate was calculated as [(target region/reference region)-1]. In this study, the mean DAT binding scores (DATbs) of the caudate nucleus were used as DATbs.

Statistical Analysis

We used IBM Statistical Package for Social Sciences (SPSS) v26.0 software for all analyses. To investigate whether the caudate nucleus DATbs mediates the relationship between age and cognition, we applied the mediation model proposed by Hayes using the SPSS PROCESS macro (35). In this mediation model, the indirect effect is the impact of the independent variable (age) on the outcome variable (cognitive functions) through the mediator variable (caudate DATbs), while the direct effect is the impact of the independent variable on the outcome without considering the mediator. The total effect (c) is calculated as the sum of the direct (c') and indirect effects (ab) (Figure 1). We included gender and years of education as covariates in the model to account for their potential influence on the DATbs and cognitive outcomes in PD (36,37). To test the significance of indirect effects, we used a bootstrapping procedure with 5,000 samples. This method provides point estimates of the indirect effect and 95% confidence intervals. Indirect effects were considered significant when the 95% confidence interval did not contain zero (38). The significance level was set at <0.05.

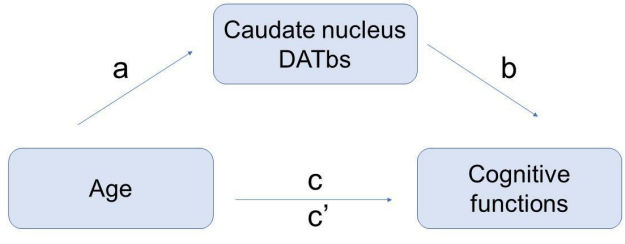

Figure 1: Simple mediation model. a, The effect of age on caudate nucleus DATbs; b, The effect of caudate nucleus DATbs on cognitive functions; c, The total effect of age on cognitive functions; c', The direct effect of age on cognitive functions

DATbs: Dopamine transporter binding scores

Results

In this study, data from 1,099 PD patients, including demographic, cognitive, and neuroimaging data, were analyzed. Participants had an average age of 62.64 (±9.56) years, and 41.2% were female. The demographic and clinical information of the participants, along with the cognitive test results, are presented in Tables 1 and 2, respectively.

Table 1: Demographic and clinical characteristics of patients

Age	62.64±9.56
Sex, n (%)	
Female Male	466 (41.2%) 663 (58.8%)
Hand preference, n (%)	
Right-handed Left-handed Ambidextrous	997 (88.3%) 93 (8.2%) 36 (3.2%)
Education years (year)	16.06±3.47
Diagnosis time (day)	406.12±634.75
Symptom time (day)	1338.94±3805.94
Caudate nucleus DATbs	0.86±0.33

Values are presented as %, mean (SD)
SD: Standard deviation, DATbs: Dopamine transporter binding scores

Table 2: Cognitive test scores

Trail Making Test-A (s)	40.54±21.45
Digit Symbol Substitution Test	42.39±10.80
Semantic Fluency	32.44±16.22
Number Letter Sequencing Test	4.05±5.36
Hopkins Verbal Learning Test	18.30±23.77
Line Orientation Test	9.70±12.51
Montreal Cognitive Assessment	26.76±2.62

Values are presented as mean (SD). TMT-A score represents the time required to complete the test, while the scores on all other tests denote accuracy
TMT-A: Trail Making Test-A, SD: Standard deviation, s: In seconds

The analysis revealed a significant total effect of age on TMT-A, indicating that older age was associated with a longer completion time (c=0.4487, standardized error (SE): 0.0658, p<0.001). Additionally, the direct effect of age on TMT-A remained significant (c'=0.4301, SE: 0.0660, p<0.001), suggesting partial mediation. The total effect of age on DSST was significant, and older age was associated with lower scores (c=-0.4362, SE: 0.0303, p<0.001). The direct effect of age on DSST was also significant, indicating partial mediating effect (c'=-0.4203, SE: 0.0302, p<0.001). The total effect of age on SFT was significant, and older age was associated with lower scores (c=-0.3596, SE: 0.0498, p<0.001). The direct effect of age on SFT was also significant, indicating partial mediating effect (c'=-0.3759, SE: 0.0499, p<0.001). The total effect of age on NLST was significant, and older age was associated with lower scores (c=-0.1124, SE: 0.0165, p<0.001). The direct effect of age on NLST was also significant, indicating partial mediating effect (c'=-0.1175, SE: 0.0166, p<0.001). The total effect of age on HVLT was significant, and older age was associated with lower scores (c=-0.3156, SE: 0.0741, p<0.001). The direct effect of age on HVLT was also significant, indicating partial mediating effect (c'=-0.3397, SE: 0.0743, p<0.001). The total effect of age on LOT was significant, and older age was associated with lower scores (c=-0.2144, SE: 0.0388, p<0.001). The direct effect of age on LOT was also significant, indicating partial mediating effect (c'=-0.2277, SE: 0.0388, p<0.001). The total effect of age on MoCA was significant, with older age associated with lower scores (c=-0.0732, SE: 0.0078, p<0.001). The direct effect of age on MoCA remained significant after accounting for the mediator (c'=-0.0715, SE: 0.0078, p<0.001), while the indirect effect was not significant. Table 3 presents the results of the simple mediation analysis, showing the total and direct effects on cognitive functions. Accordingly, caudate nucleus DATbs partially mediated the effect of age on TMT-A, DSST, SFT, NLST, HVLT, and LOT scores. Table 4 summarizes the caudate nucleus DATbs mediation findings for the effect of age on cognitive functions (indirect effects).

Table 3: Total and direct effects of age on cognitive functions

Cognitive tests	Total effect			Direct effect		
	β	SE	p	β	SE	p
TMT-A	0.4487	0.0658	<0.001	0.4301	0.0660	<0.001
Digit Symbol Substitution Test	-0.4362	0.0303	<0.001	-0.4203	0.0302	<0.001
Semantic Fluency	-0.3596	0.0498	<0.001	-0.3759	0.0499	<0.001
Number Letter Sequencing Test	-0.1124	0.0165	<0.001	-0.1175	0.0166	<0.001
Hopkins Verbal Learning Test	-0.3156	0.0741	<0.001	-0.3397	0.0743	<0.001
Line Orientation Test	-0.2144	0.0388	<0.001	-0.2277	0.0388	<0.001
Montreal Cognitive Assessment	-0.0732	0.0078	<0.001	-0.0715	0.0078	<0.001

β: Unstandardized regression coefficient
TMT-A: Trail Making Test-A, SE: Standardized error, p: Statistical significance

Table 4: Indirect effect findings			
Cognitive tests	β	95% CI	
		LLCI	ULCI
Trail Making Test - A	0.0186	**0.0036**	**0.0385**
Digit Symbol Substitution Test	-0.0160	**-0.0293**	**-0.0061**
Semantic Fluency	0.0163	**0.0042**	**0.0336**
Number Letter Sequencing Test	0.0051	**0.0011**	**0.0106**
Hopkins Verbal Learning Test	0.0241	**0.0061**	**0.0493**
Line Orientation Test	0.0133	**0.0037**	**0.0268**
Montreal Cognitive Assessment	-0.0017	-0.0042	0.0001

Bold indicates significant mediation effects
β: Unstandardized regression coefficient
LLCI: Lower level confidence interval, ULCI: Upper level confidence interval

Discussion

This study demonstrated that the effect of age on cognitive functions in patients with PD is mediated by caudate nucleus dopaminergic activity. This finding suggests that caudate nucleus dopaminergic activity may be an important factor in explaining age-related cognitive decline in PD patients.

The cognitive tests in which caudate nucleus dopaminergic activity showed a significant mediation effect were TMT-A, DSST, Semantic Fluency Test, Number Letter Sequencing Test, Hopkins Verbal Learning Test and Line Orientation Test, which assess attention-executive functions, processing speed, verbal function, working memory, verbal episodic memory, and visual-spatial functions, respectively.

The caudate nucleus plays a crucial role in the cortico-striato-thalamic-cortical circuit, serving as a central hub for information processing (39) and playing a key role in cognitive functions (40). Research has demonstrated a connection between DAT binding in the caudate nucleus and cognition, with longitudinal studies suggesting that this binding may be a predictor of future cognitive decline (20,41,42). Relatedly, this study's results align with previous research indicating that attention, working memory, processing speed, verbal fluency, verbal memory, and visuospatial functions are linked to dopaminergic activity within the caudate nucleus (19,21,43,44).

Supportingly, studies have shown that the decline in dopamine levels plays a crucial role in the impact of aging on cognitive function (45,46). Regarding PD, observations have highlighted that individuals with cognitive impairment exhibit lower striatal DAT binding, indicating a more pronounced dopamine denervation compared to those without cognitive impairment (19,31,47).

The precise role of dopaminergic regulation in cognition is not completely understood, but it is believed to affect cognitive functions through the nigrostriatal pathway and mesocortical dopaminergic projections (48,49). There is a dopaminergic connection between the substantia nigra and striatum in the nigrostriatal pathway, as well as between the ventral tegmental area and prefrontal cortex in the mesocortical pathway. Physiologically regulated dopamine neurotransmission is important for the proper functioning of these dopaminergic pathways. Diminished dopaminergic neurons and/or dopamine neurotransmitter levels may result in impaired connectivity between regions and possibly underlie cognitive dysfunction.

It is important to note that the striatum exhibits a topographical organization and has reciprocal connections with the neocortex. Changes in any part of the frontostriatal network can lead to structural and functional changes in other parts. Studies have shown that stimulating the dorsolateral prefrontal cortex increases neural activity and dopamine release in the caudate nucleus, indicating a connection between executive frontal areas and the caudate nucleus (50). Therefore, the association observed in this study between memory, visuospatial function, and the presence of DAT in the caudate nucleus may indicate a disruption in frontostriatal dopaminergic function. It is also worth noting that memory and visuospatial dysfunctions in PD are thought to be secondary to impairments in working memory and executive function (51).

Finally, the caudate nucleus receives indirect anatomical connections from the superior colliculus, a midbrain structure recognized for its key role in controlling visual attention (52). This structural relationship may help to explain how reduced dopamine levels in the caudate nucleus mediate the regulation of visual attention.

Unlike other cognitive assessments, this study found no significant mediation effect of caudate nucleus DATbs on the relationship between age and the MoCA score. One possible explanation is that as a global cognitive assessment tool, MoCA provides an overall measure of cognitive function across various domains, whereas the other assessments are more domain-specific. While MoCA is valuable for detecting mild cognitive impairment, it may not be sensitive enough to detect specific cognitive processes that depend on caudate nucleus function or dopaminergic activity. Additionally, MoCA may have a ceiling effect, particularly in patients with less severe cognitive impairment, making it less likely to capture subtle differences in cognitive function related to dopamine levels in the caudate nucleus. As a result, in early-stage PD without significant cognitive impairment, MoCA scores may not reflect subtle cognitive differences linked to caudate nucleus dopamine activity.

Given the cross-sectional nature of this study's design, it is important to consider the hypothesis that cognitive decline may occur before dopamine loss. Although most literature suggests that dopamine loss causes cognitive decline, it is

possible that cognitive decline could precede the degradation of the dopamine system through neuroplasticity and a feedback mechanism between cognition and neurotransmitter systems. This could potentially worsen both cognitive and dopaminergic impairments. Hence, this study's cross-sectional design limits the ability to establish causal relationships between age, cognitive functions, and dopamine transporter binding scores in PD. Future research should employ a longitudinal design to confirm these findings. Additionally, a regional analysis of dopaminergic activity in the caudate nucleus and its relationship with cognitive functions could provide more detailed insights. Lastly, further studies are needed to elucidate the impact of anomalies in other neurotransmitter systems in mediating cognitive function losses in PD.

Conclusion

This study provides insights into the interplay between age, cognitive function, and dopaminergic activity in the caudate nucleus, offering potential implications for the monitoring and managing of cognitive symptoms in PD. Further longitudinal studies are warranted to validate the mediating role of dopaminergic activity in cognitive decline and its clinical relevance for PD patients.

Ethics

Ethics Committee Approval: The PPMI protocol was reviewed and approved by the Institutional Review Board and the Independent Ethics Committee (IRB/IEC) at each center and the study followed the Guideline for Good Clinical Practice. This study obtained the right to use the PPMI database data.

Informed Consent: Each participant provided written informed consent before being included in the study.

Footnotes

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BASIC MEDICAL SCIENCES / TEMEL TIP BİLİMLERİ

Anti-Aging Effects of *Hibiscus sabdariffa* on Immortalized Human Ovarian Epithelial Cells

Hibiscus sabdariffa'nın Ölümsüz İnsan Over Epitel Hücreleri Üzerindeki Yaşlanma Karşıtı Etkileri

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Abstract

Objectives: The aim of this study is to examine the anti-aging effect of *Hibiscus sabdariffa* (HS) against oxidative stress induced by hydrogen peroxide (H_2O_2) on immortalized human ovarian epithelial cells (IHOECs).

Materials and Methods: The obtained IHOECs were combined with 12.5 mg/mL HS extracted by adding 1mL of distilled water (dH_2O) and different concentrations of H_2O_2 for oxidative effect. IHOECs cell viability was increased with HS extract and determined by MTT test assay. Real-time polymerase chain reaction was conducted to amplify and detect apoptosis-related BAX and BCL_2, stem cell markers SOX_2 and OCT_4, and antioxidative *nuclear factor erythroid 2-related factor 2* (*NRF2*) gene expressions. For the statistical analysis Kruskal-Wallis analysis and Mann-Whitney U test were used in SPSS program.

Results: The increase in HS in cell proliferation was 14%. While there is no significant increase of cell viability in the combined group with HS and H_2O_2, there were only statistically significant groups are 200, 800, 900 and, 1,000 µl. It was indicated that HS has apoptotic, stem cell promotion and antioxidative effects on high H_2O_2 concentrations of these groups ($p<0.05$).

Conclusion: In combined groups with both HS and H_2O_2 induced oxidative stress, HS increased the expression of proapoptotic gene *BAX* and decreased antiapoptotic gene BCL_2. Although, the remaining cells which are abundantly stem cells expressed genes OCT_4 and SOX_2 remarkably decreased, at high H_2O_2 concentration opposite effects were observed. NRF_2 gene expression also increased in this high oxidative stress.

Keywords: *Hibiscus sabdariffa*, oxidative stress, apoptosis, stem cells

Öz

Amaç: Bu çalışmanın amacı, *Hibiscus sabdariffa*'nın (HS) hidrojen peroksitin (H_2O_2) ölümsüzleştirilmiş insan yumurtalık epitel hücreleri (IHOEC) üzerinde neden olduğu oksidatif strese karşı yaşlanma karşıtı etkisini incelemektir.

Gereç ve Yöntem: Elde edilen IHOEC'ler, oksidatif etki için 1 mL distile su (dH_2O) ve farklı konsantrasyonlarda H_2O_2 eklenerek ekstrakte edilen 12,5 mg/mL HS ile kombine olarak denendi. IHOEC'lerin hücre canlılığının, HS ekstraktı ile arttığı MTT testi ile belirlendi. Apoptozla ilişkili BAX ve BCL_2'yi; kök hücre belirteçleri olan SOX_2 ve OCT_4'ü; antioksidatif belirteç olan *nükleer faktör eritroid 2 ile ilişkili faktör 2* (NRF_2) gen ifadelerini belirlemek için gerçek zamanlı polimeraz zincir reaksiyonu yöntemi kullanıldı. İstatistiksel analiz için SPSS programında Kruskal-Wallis analizi ve Mann-Whitney U testi kullanıldı.

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Bulgular: Hücre proliferasyonunda HS'deki artış %14 idi. HS ve H_2O_2 ile kombine edilen grupta hücre canlılığında anlamlı bir artış görülmezken, sadece 200, 800, 900 ve 1,000 µl'lik gruplar istatistiksel olarak anlamlıydı. HS'nin bu grupların yüksek H_2O_2 konsantrasyonları üzerinde apoptotik, kök hücre teşvik edici ve antioksidatif etkilere sahip olduğu belirtildi ($p<0,05$).

Sonuç: Hem HS hem de H_2O_2 kaynaklı oksidatif stresin olduğu kombine gruplarda HS, proapoptotik gen BAX'ın ekspresyonunu artırdı ve antiapoptotik gen *BCL*$_2$'yi azalttı. Geriye kalan kök hücre bakımından zengin kültürde *OCT*$_4$ ve SOX_2 genlerini ekspresyonu azalırken, yüksek H_2O_2 konsantrasyonunda tersine bir etki gözlendi. Bu yüksek oksidatif streste *NRF*$_2$ gen ekspresyonu da artış gösterdi.

Anahtar Kelimeler: *Hibiscus sabdariffa*, oksidatif stres, apoptoz, kök hücreler

Introduction

A wild tropical plant in the Malvaceae family *Hibiscus sabdariffa* (HS) is also known as roselle. There are various historical uses for HS in many cultures and established benefits of HS that are as follows: antihypertensive, anti-inflammatory, anti-obesity qualities; nephron-, hepato- and cardio- protective effects etc (1). Although further investigations are needed on its anti-aging properties, studies of this medicinal plant are still ongoing.

Immortalized human ovarian epithelial cells (IHOECs) were derived from human ovarian surface epithelium, which contains stem cells and expresses *SOX*$_2$, *OCT*$_4$ and *nuclear factor erythroid 2-related factor 2* (*NRF*$_2$) genes (2,3). We aim to investigate if and how we can use HS to slow down aging in IHOECs and improve ovarian health.

A number of the body's primary processes gradually deteriorate with age, making aging an extremely complicated process. Hereditary factors, lifestyle choices, and environmental factors including xenobiotic pollutants, infectious agents, UV radiation, diet-borne chemicals, and so forth all have an impact on this unavoidable process. Aging and senescence are accompanied by a number of internal and exterior signs and symptoms, such as wrinkles and dry skin, diabetes, atherosclerosis, cancer, and neurological diseases. The most prevalent and deadly kind of ovarian cancer is epithelial and was linked to aging in many studies. In animal models, the removal of aging cells slows or stops the aging process. It has been suggested that a reduction in mitochondrial activity causes aging because it increases reactive oxygen species (ROS) generation and macromolecule damage (4,5).

The imbalance between oxidants and antioxidants leads to oxidative stress, which is one of the primary initiating elements of aging-related damages that culminate in apoptosis. Free radicals have the ability to harm proteins, DNA, and fatty tissues in human body when their numbers exceed the antioxidants' capacity to keep them in balance. Antioxidants can prevent these processes lowering the level of oxidative stress (6).

The previous works support the scientific hypothesis that HS plants enriched with bioactive constituents play an imperative role in the management of degenerative and chronic diseases, lipid metabolism (anti-cholesterol), anti-diabetic and anti-hypertensive effects that are associated with oxidative stress (7).

Within the overall antioxidant defense strategy, the function and efficacy of the first line defensive antioxidants, such as catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD), are critical and vital. Our body's defense system against aging and oxidation is antioxidants like SOD, CAT and GPX can be enhanced by HS (8).

In this study we aimed to define the antiaging effect of HS on the IHOECs through some mechanisms and genes like *BAX*, *BCL*$_2$, *SOX*$_2$, *OCT*$_4$ and *NRF*$_2$.

In determining the survival of a cell there are many factors. There are two main routes that regulate apoptosis: the intrinsic (mitochondrial pathway) and extrinsic (death receptor pathway). The B-cell lymphoma 2 (BCL-$_2$) protein family orchestrates and regulates the intrinsic pathway. This protein family can be categorized based on their functions as either anti-apoptotic, including BCL-$_2$, BCL-x, BCL-w, MCL-$_1$, and A$_1$/BFL-$_1$, or pro-apoptotic, such as BAX, BAK. In addition, recent studies show BAX and BCL$_2$ contribute also to the cell cycle and apoptosis regulation (9).

SOX$_2$ and *OCT*$_4$ genes are embryonic stem cell markers that maintain pluripotency and regulate differentiation of stem cells. The upregulation of these genes under oxidative stress conditions with the addition of HS aqueous extract will indicate that the stem cell population is preserved. When cells transition away from a pluripotent state, SOX$_2$ signaling becomes vital for the development of various endodermal and ectodermal tissues during fetal development (10).

OCT$_4$ belongs to the Oct family of POU transcription factors. It holds a crucial position in controlling both the pluripotency and differentiation of stem cells. Considering the stem cell's role in tissues we can relate the expression of these genes to a tissue aging, the ability to regenerate and preservation (11).

NRF$_2$'s protective function extends to averting chemical- and radiation-induced carcinogenesis by facilitating the enzymatic modification and elimination of carcinogens, as well as using gene transcription to repair oxidative damage and suppress ROS. Consequently, NRF$_2$ is widely regarded as a cytoprotective transcription factor, pivotal for cellular defense mechanisms and survival. Its deficiency renders organisms more susceptible to

carcinogenesis and metastasis, highlighting its role as a tumor suppressor NRF's significance in maintaining cellular integrity and adaptation to environmental stressors (12,13).

Exposing HS, an antioxidant that uses the cascade mechanism, to the cell at an optimal level will delay the aging of the IHOECs and will extend healthy longevity. As a main result, it will prolong the reproductive age.

Materials and Methods

The cells used in the study are commercially available so ethics committee approval is not required. The study protocol was appropriate in accordance with the Declaration of Helsinki.

1. Cell Culture

IHOECs were obtained from American Type Culture Collection. IHOECs were maintained in Dulbecco's Modified Eagle's Medium/Nutrient Mixture F-12 (DMEM/F12) medium supplemented with 2.5mM L-glutamine (Bio-Ind, USA), 15mM HEPES, 100 U/mL penicillin and 100 mg/mL streptomycin (Sigma, St Louis, MO, USA) and 10% fetal bovine serum and incubated at 37 °C in humidified 5% CO_2 incubator. Every 48 hours, the growth medium was changed, and when the cells achieved 75-85% confluence, 0.25% trypsin was used to separate them.

2. HS Extract Preparation and Applying

The flower part of HS were collected and identified by the Department of Biochemistry at Ankara University Faculty of Medicine. The 12.5 mg/mL of HS were dried, mashed and extracted by adding 1 mL of dH_2O. Before applying the 12.5 mg/mL extract underwent filtration a mesh with apertures measuring 0.22 mm in diameter. Subsequently, an extract of HS was added to the cell plates and incubated for 24 hours.

3. MTT Assay

To determine the viability of IHOECs, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed. Cells were inoculated onto 96-well plates as $2x10^4$ cells per well and expected to adhere overnight. The cell groups cells were incubated with 12.5 mg/mL HS extract for 24 hours. Then they were treated with solutions of H_2O_2 within a concentration range of 200 to 800 µM and waited for 3 hours. Following this the 10 µM (5 mg/mL) of MTT reagent was introduced to each cell group for 2 hours at 37 °C. Later, 100 µL detergent reagent was added. The color change was detected by using a spectrophotometric plate reader (Biotek, USA), each sample's optical density was measured at 570 nm, using 690 nm as a reference.

4. Real-time Polymerase Chain Reaction

IHOECs cell lines being already treated were cultured in 6-well plates with seeding density of $5×10^5$ cells/well. The total RNA was isolated by Trizol reagent (Invitrogen, USA). Complementary DNA (cDNA) synthesis was carried out using reverse transcriptase (iScript cDNA synthesis kit; Biorad). To amplify and detect apoptosis-related BAX and BCL_2, stem cell marker SOX_2, OCT_4 and antioxidative NRF_2 genes Real-time polymerase chain reaction (RT-PCR) was conducted using the CFX Connect RT-PCR Detection System (Biorad, CA, USA). To normalise the expression level of mRNAs, the expression of GAPDH mRNA was used as an endogenous control. This system uses the SYBR Green PCR Master Mix (iTaq Universal SYBR Green Supermix, Biorad, CA). The amplification parameters were heating to 95 °C for 10 min, followed by 50 cycles of each denaturation to 95 °C for 30 s, annealing to 60 °C for 30 s, and extension to 72 °C for 30 s.

Statistical Analysis

The results were expressed as the mean ± standard deviation (mean ± SD) and were analysed at SPSS Statistics using Kruskal-Wallis analysis and Mann-Whitney U test. Differences with values of $p<0.05$ were considered statistically significant.

Results

1. Optimization of HS Concentration and Cell Viability Relation

By applying HS at different concentrations without exposing IHOECs to any oxidative effect, the most appropriate concentration that provided 14% maximum cell proliferation for our experiment was found to be 12.5 mg/mL HS extract, and this concentration was used in all experiments. Cell viability of IHOECs in DMEM F12 medium for 24 hours was analysed by MTT test assay. The quantitative data are presented as mean ± SD in 3 repetitive experiments ($p<0.05$) (Figure 1).

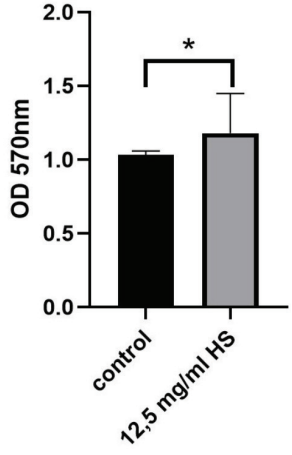

Figure 1: IHOECs cell viability without and with HS

Control: IHOECs + water; 12.5 mg/mL HS: IHOECs + 12.5 mg/mL HS

IHOECs: Immortalized human ovarian epithelial cells, HS: *Hibiscus sabdariffa*

According to Shapiro-Wilk test results, only 200, 800, 900 and 1,000 µL combined experiment results provide a test of normality (p=0.013). IHOECs were fed with HS were under oxidative influence, it was expected that a high rate of cell proliferation would be maintained due to the anti-oxidative effect of HS. Contrary to the expected results, the predicted increase in cell viability in MTT assay was not observed. MTT results indicated that cell viability in H_2O_2 and HS combined group had no significant effect on cell proliferation to change HS's anti-aging effect (p≥0.05) (Figure 2).

It has been determined that H_2O_2 at concentrations of 200 µL, 800 µL, 900 µL, 1,000 µL with HS may have a negligible antioxidant effect (p=0.05). H_2O_2 concentrations of 200 µL and 800 µL with HS showed a minor antioxidant effect and were linked to decreased cell viability, suggesting HS may alter this (Figure 2). These concentrations were further studied for their slight contribution to proliferation and potential apoptotic effects in IHOECs. They are key to demonstrating HS's impact on the expression of *SOX*$_2$, *OCT4*, *BAX*, *BCL*$_2$, and *NRF2* genes.

2. HS Treatment Protects Stem Cell Marker Gene Expressions

In the control HS group, OCT_4 and SOX_2, which are stem cell markers of survived cells, are extremely abundant. Cell lines contain a high amount of stem cell gene expressions also has been demonstrated with this experiment even without any treatment.

HS does not have an increasing effect on stem cell marker gene expression in 200 µL H_2O_2 concentrations but an increase in stem cell marker gene expressions was observed at high 800 µL concentration of H_2O_2 (Figure 3).

Although the expected anti-oxidative effect was not observed, it was observed that HS increased the *SOX*$_2$ and *OCT*$_4$ gene expression at a concentration of 800 µL, where the cells started to receive the most oxidative damage.

In the HS + 800 µL H_2O_2 group, a 4-fold increase was observed for the *OCT*$_4$ gene expression and a 5-fold increase for the *SOX*$_2$ genes under the excessive oxidative stress.

3. HS Treatment Increase the Apoptosis of Damaged Cells

Apoptosis is referred to as programmed cell death because it occurs due to biochemical instructions in the cell's DNA, is a type of protection mechanism of cells under stress (14). Apoptosis signaling is controlled by certain genes within the cell, and *BAX* (Figure 4a) is one of these apoptotic genes whereas *BCL*$_2$ is one of the anti-apoptotic genes (Figure 4b).

According to the RT-PCR reults while *BAX* gene expression increased, *BCL*$_2$ gene expression decreased. There was a strong positive correlation between HS and BAX/BCL_2 ratio. Between HS + 200 µL H_2O_2 and HS + 800 µL H_2O_2, 180-fold difference in the ratio of *BAX/BCL*$_2$ genes (Figures 4a and 4b).

This fold increase in BAX/BCL_2 proved to us that the cell was using the apoptotic pathway. The death type of cells leads that HS might protect IHOECs which under the high concentration of oxidative stress via apoptosis. In the high oxidative conditions, induction of apoptosis by the HS in the damaged cells causes clearence of vulnerable IHOECs.

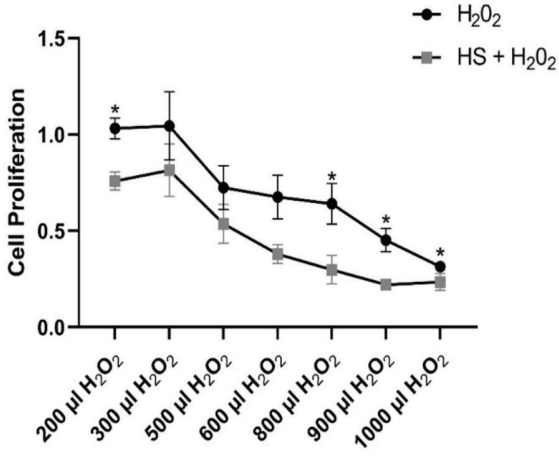

Figure 2: IHOECs proliferation in combinations of HS and different concentrations of H_2O_2

H_2O_2: IHOECs only with H_2O_2 at different concentrations; HS+ H_2O_2: IHOECs with HS and H_2O_2 at different concentrations; Mann-Whitney U test; p values ≥ 0.05 were considered statistically non-significance. Cell viability was not homogeneously distributed

IHOECs: Immortalized human ovarian epithelial cells, HS: *Hibiscus sabdariffa*

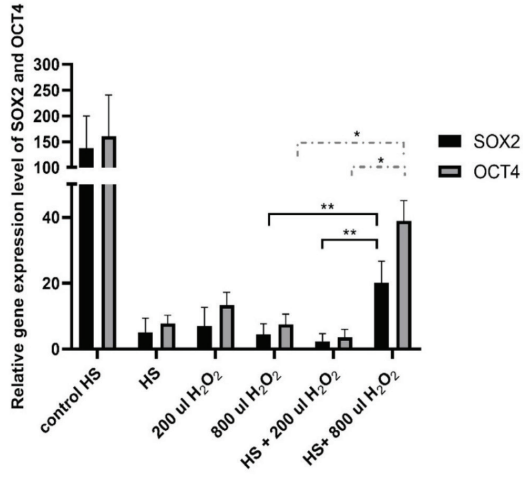

Figure 3: The expression of OCT_4 and SOX_2 genes in IHOECs in HS and different concentrations of H_2O_2, was measured by RT-PCR

control HS: IHOECs + water; HS: IHOECs + HS; 200,800 µL H_2O_2: IHOECs + H_2O_2; HS + H_2O_2: IHOECs + HS + H_2O_2; n=4; mean of 4 independent experiments are shown in the graph. All data are presented as mean ± SD. Statistical significance: *p≤0.005 (OCT4), **p≤0.001 (SOX_2)

IHOECs: Immortalized human ovarian epithelial cells, HS: *Hibiscus sabdariffa*, RT-PCR: Real-time Polymerase Chain Reaction, SD: Standard deviation

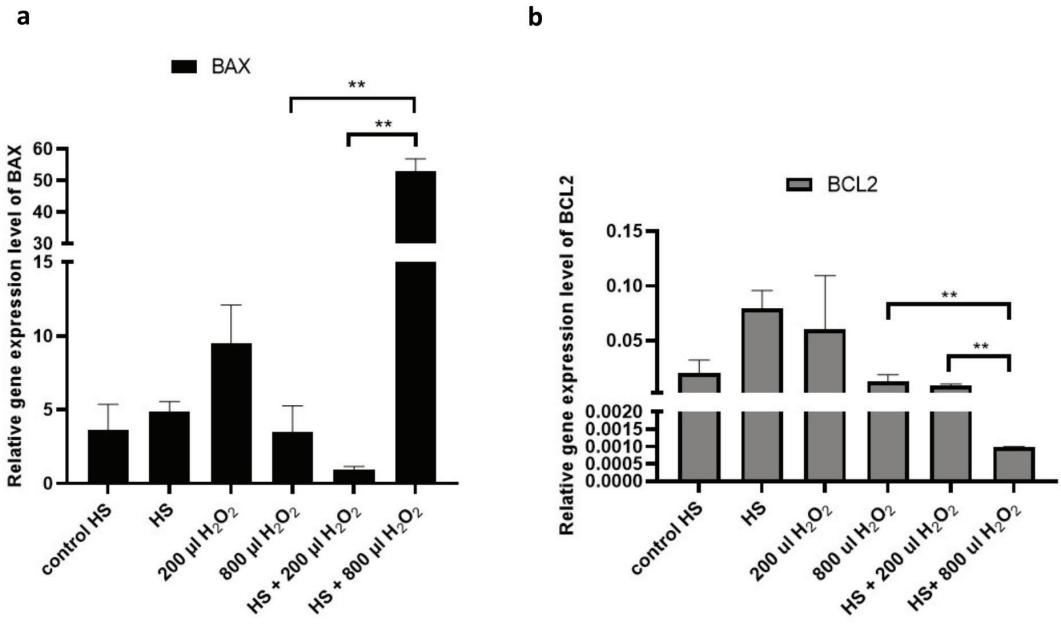

Figure 4a, b: The expression of BAX and BCL_2 genes in IHOECs in combinations of HS and different concentrations of H_2O_2, was measured by RT-PCR

n=2; mean of 2 independent experiments are shown in the figure. All data are presented as mean ± SEM (error bars). Statistical significance: *p≤0.001

IHOECs: Immortalized human ovarian epithelial cells, HS: *Hibiscus sabdariffa*, RT-PCR: Real-time polymerase chain reaction, SEM: Standard error of the mean

4. HS Treatment Increase Cellular Defence and NRF_2 Expressions in High Concentrations

The transcription factor NRF_2 controls the production of genes involved in drug detoxification and the oxidative stress response, which in turn protects cells against toxic and oxidative assaults. Cells become resistant to inflammatory stimuli and chemical carcinogens when NRF_2 is activated (15).

In this four repetitive *NRF_2* gene expression determination in different concentration of H_2O_2 (200 µL H_2O_2 and 800 µL H_2O_2) experiment, there is any effect of HS in terms of cell proliferation in the control group or cellular defence against 200 µL H_2O_2 applied group (Figure 5).

Also, there is a higher expression rate in HS + 800 µL H_2O_2 than HS + 200 µL H_2O_2. These results indicate that HS may be more effective in terms of anti-oxidative and cellular defence effects in high concentration compared to low concentrations. P<0.001 indicates there was strong significance difference (Figure 5).

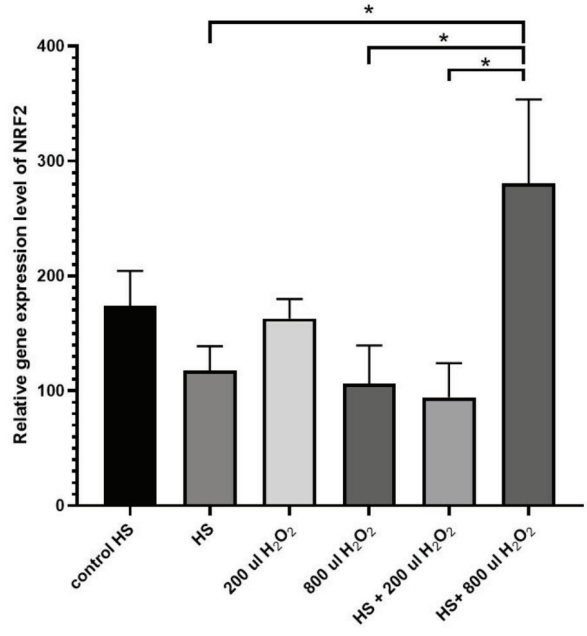

Figure 5: The expression of NRF_2 in IHOECs in combinations of HS and different concentrations of H_2O_2, was measured by RT-PCR

n=4; mean of 4 independent experiments are shown in figure. All data are presented as mean ± SD. Statistical significance: *p≤0.001 (NRF_2)

IHOECs: Immortalized human ovarian epithelial cells, HS: *Hibiscus sabdariffa*, RT-PCR: Real-time polymerase chain reaction, SD: Standard deviation, NRF_2: Nuclear factor erythroid 2-related factor 2

Discussion

HS is a rich source of bioactive compounds which makes it a significantly rewarding topic of research. In recent literature, it is found to have many effects including antiseptic, diuretic, antioxidant and antimutagenic properties (16).

The anti-aging and antitumoral effects of HS were investigated on different types of cells including fibroblasts of skin (17), breast cells (18) and to name few.

However, IHOECs cell lines were not commonly studied until our study, although we see many examples of similar cell lines such as immortalized human ovarian surface epithelial cells.

The expected anti-oxidative effect of HS was not observed when the cells were under oxidative influence. Despite the anticipation that HS would maintain a high rate of cell proliferation due to its anti-oxidative effect, an increase in cell viability was not observed. This suggests that while HS may have some antioxidant properties, its effectiveness may be limited to concentrations of oxidative stress.

None of the previous studies in the literature examined stem cell properties in IHOECs. With this study, we examined the basal levels of *SOX*$_2$ and *OCT*$_4$ genes which have embryonic stem cell pluripotency in IHOECs for the first time and showed with our experiments that these cells contain stem cells.

It is known that ovarian epithelial cells are an important source of stem cells. Before being used therapeutically, it must have the proliferative potency and the capacity to maintain stem cells and progenitor cells without undergoing genetic modification during *ex vivo* culture (19).

In the context of IHOECs, in addition to showing high expression in the control group, it was observed that *SOX*$_2$ and *OCT*$_4$ gene expressions decreased dose-dependently only under the influence of H_2O_2. However, when the oxidative stress in the cells was increased following HS treatment application, an increase in the expression of stem cell biomarkers was observed. Cell death was observed in the group in which 200 µL of H_2O_2 was applied together with HS solution and it was stated that stem cell markers decreased. In the group where 800 µL $H_20_2$was applied together with HS solution, although cell death was observed, the expression of stem cell markers increased.

The increase in the expression of SOX_2 and OCT_4 in the presence of high oxidative stress following HS treatment, may provide evidence that HS solution has a protective effect on stem cells in IHOEC.

An increase in stem cell markers could suggest a pre-cancerous effect due to potential DNA damage under high oxidative stress. To verify this, DNA damage should be assessed in these cells under varying oxidative stress levels.

We studied the cell death mechanism in IHOEC due to oxidative stress, a topic not previously explored. We found a significant increase in BAX, a protein that promotes cell death, and a notable decrease in BCL_2, a protein that prevents it. This suggests a high BAX/BCL_2 ratio and indicates apoptosis in the IHOECs.

NRF_2, a cellular oxidative stress sensor, increases the cell's antioxidant capacity by upregulating genes to eliminate ROS (20,21). HS enhances antioxidant defense by reducing ROS and increasing SOD and CAT (22). Our results show NRF_2 expression decreased at low stress but increased at high stress, indicating HS's antioxidant effect at high oxidative stress. Contrary to studies showing NRF_2 upregulates BCL_2 and downregulates BAX (23), our study found an exponential increase in BAX/BCL_2. A study found boric acid's antioxidant and antineoplastic effects on damaged cells by increasing NRF_2 and BAX/BCL_2 (24). Similarly, HS may activate NRF_2 pathway and stimulate apoptosis in stressed IHOEC cells. Parallel to our study, HS may have an antioxidant effect on IHOEC cells by the activation of the NRF_2 antioxidant pathway and stimulation of apoptotic death of the stressed cells.

Nevertheless, in other studies, NRF_2 was found to play an unexpected role in cancer development (25,26). Related to that, an increase in the expression of NRF_2 may be related to the initiation of cancer in the epithelial ovarian cells.

It was found significantly in our study that H_2O_2 application reduced the number of cells. Results can conclude that in the presence of high oxidative stress, HS has the potential to preserve the viability of stem cells while driving normal cells to apoptosis. Since maintaining the viability of stem cells is critical for tissue regeneration and repair, we can say that HS has a positive effect on the general condition of IHOEC.

The effect of HS impact on gene expression and its potential geno-protective effects make it a promising area for further research. Future studies could explore these effects in more detail, potentially uncovering new therapeutic applications for HS. These findings contribute to our understanding of the complex interactions between plant extracts, oxidative-stress, cell viability, stem cell protection and open new avenues for research in this area.

From an alternative perspective, adult-onset ovarian cancer and neo-oogenesis may be caused by stem cells found in IHOECs. This situation may indicate that it controls neo-oogenesis in addition to the pathophysiology of epithelial ovarian cancer. Thus, ovarian cancer and epithelial stem cells are closely related. As a result, a model can be developed to investigate the initial stages of ovarian cancer and produce novel insights.

Conclusion

In conclusion, this study suggests that adding HS to IHOEC during culture has the potential to cause clearance of damaged cells and induce stemness of IHOECs for the first time. It was reported that HS stimulated apoptosis in highly oxidative damaged cells and cause an increase in stem cell markers.

Ethics

Ethics Committee Approval: The cells used in the study are commercially available so ethics committee approval is not

required. The study protocol was appropriate in accordance with the Declaration of Helsinki.

Informed Consent: The cells used in the study are commercially available so informed consent was not obtained.

Footnotes

Authorship Contributions

Laboratory Practices: E.D.K., Y.N.P., Concept: A.S., E.D.K., Y.N.P., Design: A.S., E.D.K., Y.N.P., A.G.B., N.Ö., N.F., Data Collection and/or Processing: Y.N.P., T.Y., M.Ç., D.G., T.Ö., Analysis and/or Interpretation: Y.N.P., T.Y., M.Ç., T.Ö., Literature Search: Y.N.P., T.Y., M.Ç., S.A., H.A., A.I., Writing: E.D.K., Y.N.P., T.Y., M.Ç., S.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Relationship of Frailty and Nutritional Status with Laboratory Parameters in Older Adults Admitted to the Emergency Department

Acil Servise Başvuran Yaşlılarda Kırılganlık ve Beslenme Durumunun Laboratuvar Parametreleri ile İlişkisi

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Abstract

Objectives: Frailty and malnutrition in older adults are associated with many adverse outcomes. Our study aimed to compare malnutrition and frailty scales and laboratory test results in older adults admitted to the emergency department

Materials and Methods: This single-center cross-sectional study was conducted in the emergency department of a university hospital. The frailty status of the patients was evaluated with the clinical frailty scale (CFS), and the patients were grouped as frail and non-frail. Mini nutritional assessment-short form (MNA-SF) evaluated malnutrition status. The patients were grouped as malnourished, malnutrition risky, and normal nutritional status. In addition to the basic biochemical parameters of the patients, prealbumin, iron, fasting insulin, hemoglobin a1c, vitamin B12, and parathyroid hormone levels were measured. The relationship between laboratory results and CFS and MNA-SF results was analyzed statistically.

Results: One hundred-six patients were included in the study. Sixty-six patients were female, and the mean age was 78.1±7.43 years. According to the CFS scale, 87.7% of the patients were found to be frail. According to MNA-SF, the rate of patients was 18.9% malnourished and 47.2% at risk of malnutrition. When the scales and laboratory results were compared, frail patients had lower levels of prealbumin, iron, total protein, hemoglobin, and sodium, which was statistically significant. In malnourished patients, prealbumin, fasting insulin, total protein, albumin, hemoglobin, and calcium levels were lower.

Conclusion: In our study, we think that laboratory parameters can help in the early diagnosis of frailty and malnutrition.

Keywords: Frailty, malnutrition, older adults, emergency medicine

Öz

Amaç: Yaşlı yetişkinlerde kırılganlık ve yetersiz beslenme birçok olumsuz sonuçla ilişkilidir. Çalışmamızda acil servise başvuran yaşlı yetişkinlerde malnütrisyon ve kırılganlık ölçekleri ile laboratuvar test sonuçlarının karşılaştırılması amaçlandı.

Gereç ve Yöntem: Bu tek merkezli kesitsel çalışma bir üniversite hastanesinin acil servisinde gerçekleştirildi. Hastaların kırılganlık durumu klinik kırılganlık ölçeği (CFS) ile değerlendirildi ve hastalar kırılgan ve kırılgan olmayan olarak gruplandırıldı. Mini beslenme değerlendirmesi-kısa formu (MNA-SF) yetersiz beslenme durumunu değerlendirdi. Hastalar malnütrisyonlu, malnütrisyon riskli ve beslenme durumu normal olarak gruplandırıldı. Hastaların temel biyokimyasal parametrelerinin yanı sıra prealbümin, demir, açlık insülini, hemoglobin a1c, B12 vitamini ve paratiroid hormon düzeyleri ölçüldü. Laboratuvar sonuçları ile CFS ve MNA-SF sonuçları arasındaki ilişki istatistiksel olarak analiz edildi.

Bulgular: Çalışmaya 106 hasta dahil edildi. Hastaların 66'sı kadındı ve yaş ortalaması 78,1±7,43 yıldı. CFS skalasına göre hastaların %87,7'sinin kırılgan olduğu belirlendi. MNA-SF'ye göre yetersiz beslenen hastaların oranı %18,9, yetersiz beslenme riski taşıyanların oranı ise %47,2 oldu. Ölçekler ve laboratuvar sonuçları karşılaştırıldığında, kırılgan hastalarda prealbümin, demir, total protein, hemoglobin ve sodyum düzeyleri istatistiksel olarak anlamlı derecede düşüktü. Yetersiz beslenen hastalarda prealbümin, açlık insülini, toplam protein, albümin, hemoglobin ve kalsiyum düzeyleri daha düşüktü.

Sonuç: Çalışmamızda laboratuvar parametrelerinin kırılganlık ve malnütrisyonun erken teşhisinde yardımcı olabileceğini düşünüyoruz.

Anahtar Kelimeler: Kırılganlık, malnütrisyon, yaşlılar, acil tıp

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Introduction

Older adults are defined as individuals aged 65 and over (1). Thanks to the developments in medicine, the number and rate of older adults are increasing in all countries, and the number of older adults is expected to double by 2050 (2). The term "geriatric syndrome" is used to emphasize the characteristics of the health status of older adults (3). The most common geriatric syndromes are frailty, malnutrition, depression, falls, sarcopenia, dementia, dizziness, multiple drug use, urinary incontinence, and pressure ulcers (4,5). Among these syndromes, frailty, and malnutrition are thought to be the most critical factors in increased morbidity and mortality (6).

Frailty is a state of increased vulnerability to poor resolution of homeostasis after a stressor (7). Many scoring systems, such as modified frailty index, FRAIL scale, and clinical frailty scale (CFS), have defined frailty (8). CFS is based on functional status and underlying comorbidities (9). CFS has advantages over other scales in assessing vulnerability, such as ease of implementation and no requirements for complex surveys. It was also demonstrated that the CFS serves as a rapid, reliable, and valid screening tool for assessing frailty in Turkish older adults (10).

Malnutrition is a decrease in the physical and cognitive functions of the body due to deficiencies in nutrient intake (11). Several scales such as nutritional risk screening, mini nutritional assessment-short Form (MNA-SF), and malnutrition universal screening tool are used to determine malnutrition (12,13). The MNA-SF demonstrated a sensitivity of 94% and a specificity of 81% for malnutrition screening in Turkish older adults, indicating its effectiveness as a diagnostic tool for this demographic (14).

In the literature, studies concerning the relationship between malnutrition and frailty scores and laboratory parameters such as D-dimer, fibrinogen, hemoglobin, albumin, prealbumin, total lymphocyte count, vitamin B12, or folate have been widely published (8,15,16). However, some parameters have not yet been included; iron, parathyroid hormone (PTH), insulin, and hemoglobin a1c (HbA1c) may relate to malnutrition and frailty. Literature studies show that frailty and malnutrition are associated with adverse outcomes such as falls, functional decline, emergency department (ED) admission, hospitalization, and mortality (17,18). Early detection of older adults at risk of experiencing such adverse outcomes may facilitate timely and targeted intervention. An easily reproducible and objective parameter may lead to the management of frail or malnourished older adults. Therefore, we aimed to compare the malnutrition and frailty scales and laboratory test results in older adults admitted to the ED.

Materials and Methods

Study Design and Setting

This cross-sectional and prospective study, a single-center, was conducted in the ED of a tertiary university hospital. Patients aged 65 and over, admitted to the ED between 01.09.2022 and 01.11.2022, with traumatic or non-traumatic reasons, were included in the study. This study was approved by the Local Ethics Committee of Ankara University Faculty of Medicine (decision no.: İ07-424-22, date: 04.08.2024) and this study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Patients aged 65 and over, regardless of gender, who could act independently or with support and whose consent to participate in the study could be obtained from themselves or their legal guardians, were included in the study. Patients with moderate to severe Alzheimer's/dementia who received treatment for malignancy in the last six months, were immobile, had multiple traumas, and did not want to participate were excluded from the study. Age, gender, alcohol and smoking habits, medication use, and comorbid diseases in the population group were recorded. The frailty status of the patients was evaluated with CFS. Patients with a score of four or more on the CFS were considered frail.

The malnutrition status of the patients was evaluated with MNA-SF. If the total score obtained from MNA-SF was between 0 and 7, the patient was considered malnourished; if it was between 8-11, the patient was considered to be at risk of malnutrition; and if it was between 12-14, the patient was considered not malnourished.

In addition to the blood tests taken related to the patient's complaints on admission to the ED, prealbumin, iron, fasting insulin, HgA1c, vitamin B12, and PTH levels were measured without any additional charge from the patients or their social service institutions.

Statistical Analysis

IBM SPSS Statistics 26.0 program was used to analyze the data. Frequency and percentage, mean and standard deviation, and median (minimum and maximum or interquartile distribution range) were calculated as descriptive statistics. For comparisons between groups, chi-square or Fisher's exact chi-square test for categorical variables, Student's t-test for continuous variables or post-hoc Tukey test with One-Way Analysis of Variance, Mann-Whitney U or Kruskal-Wallis for non-normally distributed and ordinal variables Wallis analysis of variance was used. If there was a difference between the groups due to Kruskal-Wallis analysis of variance, Dunn's test was used to determine which group differed from which. Pearson's or Spearman's correlation

coefficient was used to determine the relationship's direction and strength between the variables. Multiple logistic regression analysis was applied to determine the factors affecting outcome variables. The odds ratio and 95% confidence interval were used as correlation coefficients. Those with a p-value less than 0.05 were considered statistically significant.

Results

A total of 106 patients were included in the study. The flow chart of the patients included in the study is shown in Figure 1.

Of the 106 patients included in the study, 66 were female, 40 were male, and the mean age was 78.1±7.43 years. While 1 (0.9%) of the patients used alcohol, 7 (6.6%) were active smokers. Calcium channel blockers and oral anti-diabetic were the most commonly used drugs. The most common diseases were hypertension (n=92, 86.8%), diabetes mellitus (n=42, 35.6%), congestive heart failure (n=40, 37.7%), asthma/chronic obstructive pulmonary disease (n=27, 25.5%), coronary artery disease (n=33, 31.1%), moderate/severe renal disease (n=29, 27.4%). Among other diseases, cerebrovascular disease (n=7,6.6%), dementia (n=5, 4.7%), depression (n=4, 3.8%), peripheral vascular disease (n=4, 3.8%), rheumatological disease (n=2, 1.9%), peptic ulcer (n=3, 2.8%), non-metastatic tumor (n=9, 8.5%), leukemia (n=2, 1.9%), lymphoma (n=2, 1.9%), moderate/severe liver disease (n=1, 0.9%) and, metastatic tumor (n=5, 4.7%) were less frequent diagnosed diseases (Table 1).

The number of patients considered frail according to the CFS scale was 93 (87.7%). According to MNA-SF, the number of patients with a score between 0-7 and accepted as malnourished was found to be 20 (18.9%), and the number of patients with a score between 8-11 and accepted as at risk of malnutrition was found to be 50 (47.2%).

When comparing laboratory parameters with CFS a statistically significant correlation was found for prealbumin (r=-0.31, p=0.03), iron (r=-0.24, p=0.04), total protein (r=-0.42, p=0.01), hemoglobin (r=-0.40, p=0.01), and sodium (r=-0.19, p=0.01). Frail patients had lower prealbumin, iron, total protein, hemoglobin, and sodium levels (Table 2).

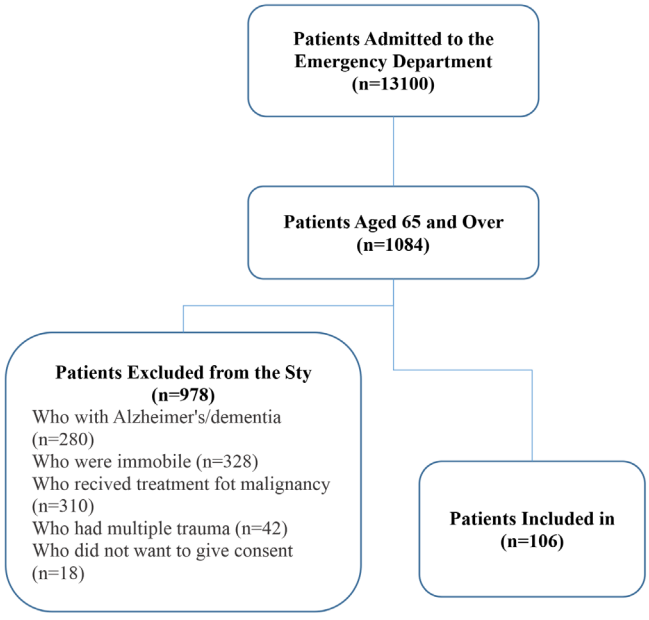

Figure 1: Flow chart of the study

Table 1: Demographic data of the patients	
	n (%)
Total number of patients	106 (100)
Age (median± SD)	78.1±7.43
Gender	
Woman	66 (62.3)
Man	40 (37.7)
Alcohol use	
Yes	1 (0.9)
No	105 (99.1)
Smoking	
Yes	7 (6.6)
No	99 (93.4)
Medications	
Statin	29 (27.4)
Furosemide	32 (30.2)
Thiazide	36 (34.0)
Calcium channel blocker	45 (42.5)
OAD	38 (35.8)
PPI	3 (2.8)
Warfarin	4 (3.8)
Comorbid diseases	
CHF	40 (37.7)
Asthma/COPD	27 (25.5)
HT	92 (86.8)
MI	33 (31.1)
Moderate/severe kidney disease	29 (27.4)
DM	42 (24.5)
Others	36 (34.0)
CFS	
Frail	93 (87.7)
Not frail	13 (12.3)
MNA-SF	
0-7 malnourished	20 (18.9)
8-11 risk of malnourished	50 (47.2)
12-14 normal nutritional status	36 (34.0)

CHF: Congestive heart failure, COPD: Chronic Obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, CFS: Clinical frailty scale, MNA-SF: Mini nutritional assessment-short form, SD: Standard deviation, OAD: Oral anti-diabetic, PPI: Proton pump inhibitor

Laboratory parameters were compared with one of the malnutrition scales, MNA-SF. Median values and interquartile range of the laboratory parameters of patients were malnourished (MNA-SF:0), at risk of malnutrition (MNA-SF:1), and normal nutritional status (MNA-SF:2) according to MNA-SF, and p values are shown in Table 3. After finding statistically significant results, pairwise comparisons were made.

When MNA-SF and low prealbumin levels were compared, a statistically significant difference was found between malnourished patients and those at risk of malnutrition and patients with normal nutritional status. When MNA-SF was associated with low fasting insulin, a statistically significant relationship was found between malnourished patients and patients with normal nutritional status. When MNA-SF was compared with low total protein and low hemoglobin value, a statistically significant difference was found between patients with normal nutritional status and those with malnutrition risk and malnourished. When the low albumin level was compared with MNA-SF, a statistically significant difference was found about low albumin between the three nutritional groups. A statistically significant difference was found between malnourished patients and patients with normal nutritional status in the relationship between low calcium value and MNA-SF. There was no statistically significant difference between MNA-SF and values of low iron, HgA1c, total lymphocyte count, fasting blood glucose, magnesium and sodium, and high vitamin B12, PTH, D-dimer, neutrophil-lymphocyte ratio, creatinine clearance (CrCl) and phosphorus. In malnourished patients, prealbumin, fasting insulin, total protein, albumin, hemoglobin, and calcium levels were lower (Table 3).

The univariate logistic regression analysis indicated that prealbumin, total protein, hemoglobin, and fasting blood glucose levels showed significant relationships with CFS and prealbumin, total protein, albumin, hemoglobin, and calcium levels showed significant associations with MNA-SF ($p<0.05$) (Table 4).

Table 2: Participants' characteristics by CFS subgroups

	Not frail patients	Frail patients	p-value
Age (mean ± SD)	74.38±7.78	78.66±7.26	0.59
Gender n, (%)			0.2
Female	6 (46.2%)	60 (64.5%)	
Male	7 (53.8%)	33 (35.5%)	
Laboratory parameters (median/IQR)			
Prealbumin (g/L)	0.23/0.07	0.17/0.11	**0.03**
Iron (µg/dL)	64/64	41/43	**0.04**
Fasting insulin (µIU/mL)	11.9/12.3	9.4/13.8	0.58
Vitamin B12 (pg/mL)	330/225.5	383/371	0.13
HbA1c (%)	6.1/1.0	6.1/1.4	0.41
Parathormone (pg/mL)	59/56	54/63	0.58
Total protein (g/L)	70.3/8.6	63.3/12.6	**<0.01**
Albumin (g/L)	42.0/6.0	38.10/7.7	0.08
D-dimer (ng/mL)	455/695	462/606	0.90
Total lymphocyte count ($x10^{n9}$/L)	1.95/1.34	1.39/1.06	0.06
Neutrophil lymphocyte ratio	3.09/2.45	4.24/5.55	0.06
Hemoglobin (g/dL)	13.0/2.9	11.3/3.1	**<0.01**
Fasting blood glucose (mg/dL)	102/46	124/47	0.15
CrCl (mg/dL)	66/37	55/41	0.38
Calcium (mg/dL)	9.0/1.0	8.8/0.81	0.09
Phosphorus (mg/dL)	2.93/1.37	3.64/1.75	0.08
Magnesium (mg/dL)	1.98/0.25	1.88/0.40	0.17
Sodium (mmol/L)	137/3	136/4	**<0.01**

IQR: Interquartile range, CFS: Clinical frailty scale, HbA1c: Hemoglobin A1c, CrCl: Creatinine clearance, SD: Standard deviation

Table 3: Participants' characteristics by MNA-SF subgroups				
	Malnourished	**At risk of malnutrition**	**Normal nutritional status**	**p-value**
Age (mean ± SD)	80.65±6.65	78.76±7.44	76.03±7.38	0.61
Gender n, (%)				
Female	11 (55%)	32 (64%)	23 (63.9%)	0.75
Male	9 (45%)	18 (36%)	13 (36.1%)	
Laboratory parameters (median/IQR)				
Prealbumin (g/L)	0.12/0.06	0.17/0.11	0.19/0.07	(MNA-SF 0-1) **0.03**
				(MNA-SF 0-2) <**0.01**
				(MNA-SF 1-2) 0.47
Iron (µg/dL)	33/27	45.5/50	49.5/49	0.08
Fasting insulin (µIU/mL)	5.6/6	9.8/12.9	13.65/14.7	(MNA-SF 0-1) 0.05
				(MNA-SF 0-2) <**0.01**
				(MNA-SF 1-2) 0.28
Vitamin B12 (pg/mL)	385/627	387/448	324/242	0.19
HbA1c (%)	5.15/1.7	6.20/1.4	6.10/1.1	0.81
Parathormone (pg/mL)	55.5/171	58/65	52.5/42	0.88
Total protein (g/L)	58.75/8.9	61.1/12.7	69.3/5.4	(MNA-SF 0-1) 0.76
				(MNA-SF 0-2) <**0.01**
				(MNA-SF 1-2) <**0.01**
Albumin (g/L)	31.55/8.5	37.55/7.4	41.1/4.1	(MNA-SF 0-1) <**0.01**
				(MNA-SF 0-2) <**0.01**
				(MNA-SF 1-2) <**0.01**
D-dimer (ng/mL)	637/1317	386/749	449/478	0.10
Total lymphocyte count (x10^{n9}/L)	1.06/0.87	1.37/1.05	1.57/0.88	0.11
Neutrophil lymphocyte ratio	6.07/7.17	4.04/5.18	3.60/4.26	0.33
Hemoglobin (g/dL)	10.75/3.3	11.15/2.0	12.95/2.8	(MNA-SF 0-1) 0.73
				(MNA-SF 0-2) <**0.01**
				(MNA-SF 1-2) <**0.01**
Fasting blood glucose (mg/dL)	112.5/89	129/60	121/34	0.15
CrCl (mg/dL)	49.5/48	57/40	64.5/42	0.59
Calcium (mg/dL)	8.65/1.92	8.8/0.11	9.05/0.70	(MNA-SF 0-1) 0.74
				(MNA-SF 0-2) **0.03**
				(MNA-SF 1-2) 0.05
Phosphorus (mg/dL)	3.69/1.58	3.67/2.01	3.20/1.22	0.05
Magnesium (mg/dL)	1.82/0.26	1.92/0.42	1.98/0.36	0.59
Sodium (mmol/L)	136/6	136/4	137/3	0.65

IQR: Interquartile range, MNA-SF: Mini nutritional assessment-short form, MNA-SF=0: Malnourished, MNA-SF=1: At risk of malnutrition, MNA-SF=2: Normal nutritional status, HbA1c: Hemoglobin A1c, CrCl: Creatinine clearance, SD: Standard deviation

Discussion

Frailty and malnutrition are significant problems that affect the level of independence and quality of life in older adults. Early diagnosis of these syndromes with the help of easy-to-access laboratory parameters may help further management of these patients. In our study, older adults who were considered frail according to CFS had lower prealbumin, iron, total protein, hemoglobin, and sodium levels; and patients who were deemed malnourished according to the MNA-SF scale had lower prealbumin, fasting insulin, total protein, albumin, hemoglobin, and calcium levels.

CFS is a common scale used in vulnerability screening. In our study, 87.7% of the patients were found to be frail, according to CFS.

Table 4: Laboratory parameters associated with CFS and MNA-SF by univariate logistic regression analysis						
	CFS			MNA-SF		
	OR	95% CI	p-value	OR	95% CI	p-value
Prealbumin (g/L)						
<0.18 vs. 0.18-0.38	7.28	1.52-34.73	**<0.01**	2.65	1.15-6.09	**0.02**
Iron (µg/dL)						
<37 vs. 37-145	2.51	0.65-9.74	0.18	1.32	0.57-3.03	0.50
Fasting insulin (µIU/mL)						
<4 vs. 4-16	3.06	0.35-26.26	0.30	4.13	0.86-19.87	0.07
>16 vs. 4-16	1.19	0.32-4.32	0.79	0.48	0.19-1.18	0.11
Vitamin B12 (pg/mL)						
<197 vs. 197-771	0.49	0.11-2.05	0.33	1.03	0.32-3.28	0.95
HbA1c (%)						
<4 vs. 4-6	1.08	0.33-3.48	0.88	1.00	0.44-2.26	0.98
Parathormone (pg/mL)						
<15 vs. 15-65	0.88	0.27-2.82	0.83	1.32	0.58-3.00	0.50
Total protein (g/L)						
<64 vs 64-83	6.39	1.34-30.45	**0.02**	12.67	4.35-36.86	**<0.01**
Albumin (g/L)						
<35 vs. 35-52	2.20	0.56-8.54	0.25	6.20	2.16-17.79	**<0.01**
D-dimer (ng/mL)						
0 vs. 0-243	1.20	0.34-4.27	0.76	1.55	0.64-3.76	0.32
Total lymphocyte count (x10^{n9}/L)						
<1.5 vs. 1.5-4	3.25	0.93-11.34	0.06	1.67	0.74-3.77	0.21
Hemoglobin (g/dL)						
<11.7 vs. 11.7-16.1	6.97	1.46-33.23	**<0.01**	3.62	1.53-8.52	**<0.01**
Fasting blood glucose (mg/dL)						
<74 vs. 74-106	3.55	1.08-11.64	**0.03**	1.44	0.60-3.46	0.41
CrCl (mg/dL)						
<60 vs. 60-120	0.98	0.96-1	0.15	1.62	0.63-2.8	0.56
Calcium (mg/dL)						
<8.6 vs. 8.6-10.2	1.29	0.33-5.07	0.71	4.44	1.40-14.01	**<0.01**
Phosphorus (mg/dL)						
<2.5 vs. 2.5-4.5	0.51	0.11-2.25	0.37	0.62	0.19-1.99	0.42
>4.5 vs. 2.5-4.5	1.74	0.34-8.85	0.49	3.59	1.11-11.62	**0.03**
Magnesium (mg/dL)	NA			2.509	0.66-9.45	0.17
Sodium (mmol/L)	NA			1.773	0.72-4.34	0.21

CFS: Clinical frailty scale, MNA-SF: Mini nutritional assessment-short form, OR: Odds ratio, CI: Confidence interval, CrCl: Creatinine clearance, HbA1c: Hemoglobin A1c, NA: Not available

On the other hand, Kaeppeli et al. (19) found the frailty rate to be 37% in a study conducted on 2,393 older adults admitted to the ED. Collard et al. (20) reported that the frailty rate ranged from 4.0 to 59.1% in a systematic review. Xu et al. (8) found that frailty can vary depending on gender, age, comorbidity, medication used, and trauma history. Our findings revealed a higher frailty rate than reported in existing literature, which we attribute to several factors. First, the study was conducted during the Coronavirus disease-2019 pandemic, a period when individuals aged 65 and older had restricted mobility, only leaving their homes for critical reasons. Second, frail older adults patients may experience extended stays in the ED, increasing their likelihood of participating in the study. Third, our ED, being a tertiary referral center, encounters a significant number of frail older adults patients with multiple comorbidities.

Protein intake is fundamental to healthy aging; frailty and its negative consequences increase in low protein intakes (21).

Hong et al. (16) and Xu et al. (8) found a statistically significant relationship between the decrease in total protein and the increase in frailty. Çevik et al. (22) also found that 71.2% of the malnourished patients had low total protein and that there was a statistically significant relationship between decreased total protein and increased malnutrition. Similar to the studies, we found that low total protein level was associated with a nearly six-fold increased risk of developing frailty and a twelve-fold increased risk of malnutrition.

Immunoglobulins (Ig) constitute about 20% of the total protein and are essential for the immune system's defense against pathogenic microorganisms (23). A meta-analysis by Khan et al. (24) revealed that older adults have reduced levels of IgM and IgG compared to their younger counterparts. Older adults with low total protein levels, who are at increased risk of frailty and malnutrition, are consequently more vulnerable to a range of complications, including infections and autoimmune disorders.

Low serum albumin, another body protein, was quite common in patients in the study group (18.9% of those with malnutrition, 47.2% of those at risk of malnutrition). Wu et al. (25) also found a statistically significant relationship between frailty and low albumin. In addition, a similar association was shown in a meta-analysis in 2020 (26). When we look at the relationship between malnutrition and low albumin, Çevik et al. (22) and Vallentini et al. (27) found a statistically significant relationship between malnutrition and low albumin. Li et al. (28) also showed that low prealbumin increased frailty. In our study, low prealbumin level was associated with an almost seven-fold increased risk of developing frailty and a two-fold increased risk of malnutrition. Based on all these results, we think that low albumin, total protein, and prealbumin can be used to predict both frailty and malnutrition.

One of the critical problems in older adults is anemia. Anemia is defined as a low level of hemoglobin that carries oxygen. Palmer et al. (29), in the systemic research they conducted, stated that there was a relationship between low hemoglobin and frailty, and frailty rate was calculated as 24% in patients with low hemoglobin. Sahin et al. (30) also showed a statistically significant relationship between malnutrition and low hemoglobin. In our study, low hemoglobin level was associated with a nearly seven-fold increased risk of developing frailty and a four-fold increased risk of malnutrition.

PTH is an important hormone that plays a role in calcium and vitamin D metabolism. In addition, PTH has functions such as regulation of bone formation. To investigate its effect on frailty, Pillatt et al. (31) found no statistically significant relationship between PTH and frailty. Although it was high in most frail patients in our study, we did not find a statistically significant relationship between frailty and PTH, similar to Pillatt et al. (31).

While vitamin B12 deficiency can be encountered with problems such as forgetfulness and numbness in the hands, studies have also shown that B12 deficiency is an element of malnutrition. Çevik et al. (22) found a statistically significant relationship between malnutrition and vitamin B12 deficiency. However, our results could not strengthen Çevik et al. (22) results since there was no significant relation between malnutrition and vitamin B12 deficiency.

The number of nephrons, renal blood flow, and glomerular filtration rate decrease with aging (32). Studies by Pillatt et al. (31) and Çevik et al. (22) reported no statistically significant association between creatinine levels and malnutrition or frailty. Given that creatinine concentrations are affected by multiple factors -including sex, age, diet, and the stage of renal impairment- relying solely on creatinine levels may introduce a margin of error when assessing renal function in older adults. Consequently, in our study, CrCl was used as the primary measure of kidney function, and no significant relationship was identified between CrCl and frailty or malnutrition. This finding is consistent with results from Yanagita et al. (33), who also observed no association between CrCl and frailty.

A notable strength of our study is its comprehensive comparison of the CFS and MNA-SF against a wide array of laboratory parameters, such as iron, PTH, fasting insulin, and HbA1c. This comparison was further supported by thorough statistical analysis utilizing logistic regression.

Study Limitations

Our study has several limitations. These can be listed as the fact that the study was conducted in a single center, there was only one researcher in data collection, the sample size was small, and there was no gold standard in evaluating frailty and malnutrition.

Conclusion

Our study demonstrated that the CFS and MNA-SF are associated with a range of laboratory parameters. When time for patient assessment is constrained in the ED, it may be beneficial for physicians to recognize that specific laboratory parameters could signal frailty or malnutrition in older adults.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Ankara University Faculty of Medicine (decision no.: İ07-424-22, date: 04.08.2024) and this study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: Informed consent was obtained from all individual participants included in this study.

Footnotes

Authorship Contributions

Concept: M.Ö.D., Y.Ç., O.P., Design: S.G., A.K., M.G., A.B.O., Data Collection or Processing: M.Ö.D., Y.Ç., Analysis or Interpretation: Y.Ç., O.P., Literature Search: M.Ö.D., Y.Ç., S.G., Writing: M.Ö.D., Y.Ç., A.K., O.P., S.G., M.G., A.B.O.

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The Relationship Between Illness Perception and Coping Strategies in Cancer Patients Undergoing Chemotherapy

Kemoterapi Alan Kanser Hastalarında Hastalık Algısı ile Başa Çıkma Stratejileri Arasındaki İlişki

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Abstract

Objectives: This study aimed to explore the relationship between illness perception and coping strategies in cancer patients undergoing chemotherapy. Given the impact of coping strategies on psychological well-being, quality of life, and treatment adherence, we aimed to address a gap in the literature by examining how illness perceptions influence coping behavior in this population.

Materials and Methods: This cross-sectional study included 282 cancer patients undergoing chemotherapy at a single center. Illness perceptions were measured using the Brief Illness Perception Questionnaire (B-IPQ), and coping strategies were assessed using the Mental Adjustment to Cancer (MAC) scale. Multivariable linear regression analyses were performed to examine the association between the B-IPQ total score and MAC subscale scores, adjusting for demographic and clinical characteristics.

Results: Negative illness perceptions were positively associated with passive coping strategies such as helplessness/hopelessness, fatalism, and anxious preoccupation, while they were negatively associated with active coping strategies such as fighting spirit. The regression models explained 21.3% of the variance in fighting spirit, 31.3% in helplessness/hopelessness, 12.4% in fatalism, and 5.8% in anxious preoccupation.

Conclusion: Our findings support the Common-sense Model of Self-regulation, demonstrating that illness perceptions are significantly associated with coping strategies in chemotherapy patients.

Keywords: Illness perception, coping, mental adjustment, cancer

Öz

Amaç: Bu çalışmada, kemoterapi alan kanser hastalarında hastalık algısı ile başa çıkma stratejileri arasındaki ilişkinin araştırılması amaçladı. Başa çıkma stratejilerinin psikolojik iyilik hali, yaşam kalitesi ve tedavi uyumuna etkisi göz önünde bulundurularak, bu popülasyonda hastalık algısının başa çıkma yöntemlerini nasıl etkilediğini inceleyerek literatürdeki bir boşluğu doldurmayı hedefledik.

Gereç ve Yöntem: Bu tek merkezli kesitsel çalışmaya kemoterapi alan 282 kanser hastası dahil edildi. Hastalık algıları Kısa Hastalık Algısı Anketi (B-IPQ) ile, başa çıkma stratejileri ise Kansere Tepki Tarzı Ölçeği (MAC) ile değerlendirildi. Demografik ve klinik özelliklere göre çok değişkenli doğrusal regresyon analizleri yapılarak B-IPQ toplam skoru ile MAC alt ölçek skorları arasındaki ilişki incelendi.

Bulgular: Negatif hastalık algısının, çaresizlik/umutsuzluk, kadercilik ve endişeli bekleyiş gibi pasif başa çıkma stratejileri ile pozitif ilişkili, mücadeleci ruh gibi aktif başa çıkma stratejileri ile ise negatif ilişkili olduğu görüldü. Regresyon modelleri, mücadeleci ruhta varyansın %21,3'ünü, çaresizlik/umutsuzlukta %31,3'ünü, kadercilikte %12,4'ünü ve endişeli bekleyişte %5,8'ini açıklamaktaydı.

Sonuç: Bulgularımız, kemoterapi hastalarında hastalık algısının başa çıkma stratejileri ile önemli ölçüde ilişkili olduğunu göstermiştir. Bu bulgular Common-sense Model of Self-regulation modelini desteklemektedir.

Anahtar Kelimeler: Hastalık algısı, başa çıkma, zihinsel uyum, kanser

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Introduction

Cancer poses significant public health problems due to its increasing global incidence and the complexity of its treatment. Approximately 20 million new cancer cases were reported in 2022, with projections suggesting that this number will reach 35 million by 2050 (1). Beyond the physical challenges of cancer treatment, the psychological and social challenges, especially the emotional burdens significantly impact patients' quality of life (2,3). Therefore, it is essential to not only consider cancer as a physical illness but also address the psychological and social aspects of patients' experiences during follow-up care.

Coping strategies refer to the cognitive and behavioral efforts individuals use to manage the stress associated with life-threatening conditions such as cancer (4). According to the stress and coping model developed by Lazarus and Folkman (5), these strategies fall into two main types: problem-focused coping and emotion-focused coping. Problem-focused coping is a constructive or active approach that involves actively confronting the illness and focusing efforts on regaining physical health and maintaining hope for recovery. In contrast, emotion-focused coping presents is a destructive or passive approach, where the illness is perceived as an overwhelming, uncontrollable threat. This leads to feelings such as anxiety, helplessness, confusion, and isolation, which ultimately results in passive surrender to the illness (6).

Leventhal's common-sense model of self-regulation explains how illness perceptions shape coping strategies. This model assumes that individuals evaluate their health status based on symptoms, beliefs, and external influences, forming cognitive and emotional representations of their illness. Shaped by personal and disease-specific factors, these representations play an important role in determining how patients cope with their illness (7).

Understanding the relationship between coping strategies and illness perceptions is critical to optimizing cancer care, as these factors can profoundly influence both treatment adherence and quality of life (8-14). Chemotherapy has significant side effects and psychological burdens, necessitating the use of active coping mechanisms to mitigate its impact on patients. However, there is a notable gap in the literature regarding the interaction between illness perceptions and coping strategies in cancer patients undergoing chemotherapy. This study aimed to address this gap by examining these dynamics and providing valuable insights that could contribute to the development of targeted and effective interventions.

Materials and Methods

Ethical approval for this study was obtained from the Ethics Committee of Ankara University Faculty of Medicine (decision no.: İ4-136-19, date: 10.10.2019). All procedures were performed in accordance with ethical standards and the principles of the Declaration of Helsinki. Signed informed consent was obtained from all patients before their inclusion in the study.

Study Design and Patients

This single-center, cross-sectional study was conducted between November 1, 2019, and April 30, 2020, at the Department of Medical Oncology of Ankara University Faculty of Medicine. The participants were informed that their decision to participate would not affect their treatment, that their personal information would be kept confidential, and that all the data would be used solely for scientific purposes.

The research team considered the potential influence of hospital environment, chemotherapy protocols, and side effects on patients' illness perceptions and coping strategies. Since cancer is a dynamic condition and coping styles may shift over time (15-17), the study focused on patients who were either undergoing chemotherapy or had completed it within the past six months. Patients undergoing salvage chemotherapy, those with cranial metastases, those with an Eastern Cooperative Oncology Group (ECOG) performance score of >2, and those with severe psychiatric disorders impairing normal communication were excluded to avoid confounding effects that could affect the analysis of coping strategies. By focusing on a more homogeneous sample of chemotherapy patients, we aimed to provide clearer insights into the relationship between illness perceptions and coping.

Data Collection

The Brief Illness Perception Questionnaire (B-IPQ) and the Mental Adjustment to Cancer (MAC) scale were used due to their importance in capturing the cognitive and emotional dimensions of illness perception and coping strategies, respectively. The researchers conducted face-to-face interviews with the patients to administer the B-IPQ and MAC scales. Special care was taken during the interviews to ensure that discussing illness perceptions and coping strategies did not exacerbate psychological distress. Immediate support was made available to any patient showing signs of distress. The demographic and clinical characteristics of the patients were also obtained from medical records.

Brief Illness Perception Questionnaire

The B-IPQ is structured to measure patients' illness perceptions and consists of several subscales that assess both cognitive and emotional representational aspects of the illness, along with the comprehensibility of the illness. For the cognitive aspects, there are five subscales: consequences (assesses the perceived effects of the illness), timeline (evaluates the patient's perception of the duration of the illness), personal control (measures the patient's

belief in their ability to control the illness), treatment control (assesses the patient's attitudes toward the effectiveness of the treatment), and identity (evaluates the perceived intensity of symptoms related to the illness). For the emotional aspects, there are two subscales: concern (gauges the level of concern the patient has about their illness) and emotions (measures the emotional impact of the illness on the patient). Additionally, the B-IPQ includes a coherence subscale that assesses the patient's sense of comprehensibility of the illness and a causal subscale where patients identify factors they believe contribute to their illness. Each subscale consists of a single question, with responses rated on an 11-point Likert-type scale ranging from 0 to 10, except for the open-ended causal subscale (18). Due to its open-ended nature, the causal subscale was not analyzed in this study. The total B-IPQ score is calculated by reversing the scores for the personal control, treatment control, and coherence subscales, and then summing them with the other subscale scores. The total score ranges from 0 to 80, with higher scores indicating a more negative illness perception. The reliability of the Turkish version of the B-IPQ was previously validated by Karataş et al. (19), with a reported Cronbach's alpha of 0.85. In the current study, the Cronbach's alpha for the B-IPQ was determined to be 0.74.

Mental Adjustment to Cancer Scale

The MAC scale is designed to measure cancer patients' coping strategies and comprises five subscales. Active coping is measured by the fighting spirit subscale (sixteen items, α=0.81), while passive coping is evaluated by the helplessness/hopelessness subscale (six items, α=0.77), anxious preoccupation subscale (nine items, α=0.54), fatalism subscale (eight items, α=0.59), and avoidance subscale (one item). The fighting spirit subscale evaluates the patient's acceptance of cancer, efforts to combat the illness, and maintenance of an optimistic perspective. The helplessness/hopelessness subscale assesses the patient's skepticism regarding their ability to control the disease, along with a pessimistic outlook and feelings of despondency. The anxious preoccupation subscale examines the patient's concerns and uncertainties about managing the disease, while the fatalism subscale assesses the patient's belief in having limited control over the progression of the disease. Lastly, the avoidance subscale evaluates the patient's inclination to deny the diagnosis. Participants respond to the questions using a four-point Likert scale (4). In a study conducted by Natan et al. (20), the reliability analysis of the Turkish version of the MAC scale showed Cronbach's alpha values ranging between 0.58 and 0.72 for the subscales. The avoidance subscale was not utilized in the current study as it consists of only one item (21).

Statistical Analysis

The normality of continuous data was assessed using the Kolmogorov-Smirnov test as well as kurtosis and skewness measures. Descriptive statistics were presented as numbers and percentages for categorical variables, and as mean ± standard deviation values for continuous variables. The reliability of the B-IPQ and MAC subscales was assessed using Cronbach's alpha. Student's t-test was used to compare continuous variables between two independent groups, and One-Way ANOVA was used for comparisons involving more than two independent groups, assuming a normal distribution. Categorical data were compared across groups using the Pearson chi-square test. Multivariable linear regression analyses were performed to assess the relationship between the total B-IPQ score and the MAC subscale scores. Each MAC subscale score was used as a dependent variable, while the B-IPQ total score was the independent variable. To control for sociodemographic and clinical characteristics, variables that were significantly associated with the MAC subscale scores were also included as independent variables in the analysis. Dummy variables were created for categorical variables such as age, sex, employment status, educational level, non-cancer comorbidities, and cancer stage. The models were checked for linearity, multicollinearity (using variance inflation factor), outliers, and normality, homoscedasticity (Breusch-Pagan test), and independence of residuals (Durbin-Watson statistic). The strength of associations between independent variables and MAC subscale scores were assessed using partial eta-squared (η^2). Eta-squared values range between 0 and 1, with η^2~0.01 indicating a small, η^2~0.06 indicating a medium, and η^2>0.14 indicating a large effect size (22). Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences software (version 26). A p-value of <0.05 was considered statistically significant.

Results

From November 1, 2019, through April 30, 2020, a total of 395 patients at the Department of Medical Oncology of Ankara University Faculty of Medicine were invited to participate in the study. Of these patients, 46 declined to participate in the study, and 67 were excluded for the following reasons: 12 had missing responses, 12 were receiving salvage chemotherapy, five had cranial metastases, 37 had an ECOG performance score of >2, and one had severe psychiatric conditions. As a result, data from a total of 282 patients were included in the statistical analysis.

Patient Characteristics

The demographics and clinical characteristics are shown in Table 1. The mean age of the patients was 57.1±13 years. Among

the 282 patients, 96 were geriatric (34%), and 152 were male (53.9%). The most prevalent type of cancer was gastrointestinal cancer (32.3%). Male sex, non-cancer comorbidities, and metastatic disease were statistically more common in geriatric patients (age ≥65 years) compared to non-geriatric patients (p=0.01, p<0.001, and p<0.001, respectively). However, university graduation and employment rates were statistically less common in the geriatric group (p<0.001 and p=0.035, respectively). There was no significant difference in the distribution of cancer types between geriatric and non-geriatric patients. Similarly, there were no significant differences between male and female patients in terms of university graduation, employment, the presence of non-cancer chronic diseases, or metastatic disease. However, the employment rate was higher among university graduates compared to those without a university degree (p<0.001).

Scale Scores

Table 2 presents the mean scores obtained from the B-IPQ and MAC scales, and Table 3 shows the comparison of the MAC subscale scores between groups. The fighting spirit score was significantly higher in non-geriatric patients, females, and employed patients compared to their counterparts (p=0.001, p=0.026, and p=0.02, respectively). The helplessness/hopelessness score was significantly higher in geriatric patients, non-employed individuals, those without a university degree, and those with non-cancer comorbidities compared to their counterparts (p=0.001, p=0.002, p=0.003, and p=0.016, respectively). The fatalism score was significantly higher among non-employed patients, those without a university degree, and those with metastatic cancer compared to their counterparts (p=0.01, p<0.001, and p=0.036, respectively). The anxious preoccupation score was significantly higher among females (p=0.031) compared to males. No significant relationship was found between coping strategies and cancer type, marital status, or receiving psychological support.

Table 1. Sociodemographic and clinical characteristics of patients

Age (M ± SD)	57.1±12.9
Male sex (n, %)	152 (53.9%)
Married (n, %)	227 (80.5%)
Employed (n, %)	53 (18.8%)
University graduate (n, %)	81 (28.7%)
Non-cancer comorbidity (n, %)	79 (28%)
Psychological support (n, %)	48 (17%)
Cancer type	
Gastrointestinal (n, %)	91 (32.3%)
Genitourinary (n, %)	53 (18.8%)
Breast (n, %)	47 (16.7%)
Lung (n, %)	58 (20.6%)
Others (n, %)	33 (11.7%)
Metastatic cancer (n, %)	156 (55.3%)
M: Mean, SD: Standard deviation	

Associations Between Illness Perception and Coping Strategies

The results of the multivariable linear regression analyses are summarized in Table 4. In the regression analysis where the fighting spirit score was taken as the dependent variable, the independent variables accounted for 21.3% of the variance [F (4,277): 18.748, R^2=0.213, adjusted R^2=0.202, Durbin-Watson: 2,109, p<0.001]. The total B-IPQ score was found to have a significant negative association with the fighting spirit score (ß=-0.209, ηp^2=0.166, p<0.001). For the helplessness/hopelessness score, the independent variables explained 31.3% of the variance [F (5,276): 25.201, R^2=0.313, adjusted R^2=0.301, Durbin-Watson: 1,970, p<0.001]. There was a significant positive association between the total B-IPQ score and the helplessness/hopelessness score (ß=0.132, ηp^2=0.260, p<0.001). When the fatalism score was taken as the dependent variable, the independent variables explained 12.4% of the variance [F (4,277): 9.763, R^2=0.124, adjusted R^2=0.111, Durbin-Watson: 2,021, p<0.001]. The total B-IPQ score demonstrated a significant positive relationship with the fatalism score (ß=0.064, ηp^2=0.058, p<0.001). In the analysis of anxious preoccupation, the independent variables explained 5.8% of the variance [F (2,279): 8.638, R^2=0.058, adjusted R^2=0.052, Durbin-Watson: 2.134, p<0.001]. The total B-IPQ score was positively associated with the anxious preoccupation score (ß=0.052, ηp^2=0.042, p=0.001).

Table 2. Scale scores

B-IPQ	
Consequences (M ± SD)	6.6±2.7
Timeline (M ± SD)	5.6±3.2
Personal control (M ± SD)	5.4±3.1
Treatment control (M ± SD)	7.9±2.2
Identity (M ± SD)	5.5±2.8
Coherence (M ± SD)	8.4±2.4
Concern (M ± SD)	6.1±3.2
Emotions (M ± SD)	6.7±3.1
Total score (M ± SD)	38.7±13.7
MAC	
Fighting spirit (M ± SD)	48.7±7
Helplessness/hopelessness (M ± SD)	11.8±3.5
Fatalism (M ± SD)	20±3.6
Anxious preoccupation (M ± SD)	23.9±3.5
B-IPQ: Brief Illness Perception Questionnaire, M: Mean, SD: Standard deviation, MAC: Mental Adjustment to Cancer Scale	

Table 3. Comparison of MAC subscales' scores between groups								
Variable	**FS**	**p-value**	**HH**	**p-value**	**FA**	**p-value**	**AP**	**p-value**
Age								
<65 years	49.7±6.7	0.001	11.3±3.4	0.001	19.7±3.7	0.052	24±3.7	0.478
≥65 years	46.9±7.2		12.8±3.7		20.6±3.6		23.7±3.1	
Sex								
Male	47.9±6.7	0.026	12±3.5	0.293	20.1±3.8	0.540	23.5±3.5	0.031
Female	49.8±7.2		11.6±3.6		19.8±3.5		24.4±3.5	
Marital status								
Married	48.6±6.8	0.348	11.7±3.5	0.633	19.9±3.6	0.641	23.9±3.5	0.847
Single/divorced	49.6±7.8		12±3.7		20.2±3.8		24±3.7	
Employment status								
Employed	50.8±6.3	0.020	10.4±3.1	0.002	18.8±3.9	0.010	10.4±3.1	0.144
Not employed	48.3±7.1		12.1±3.6		20.2±3.5		12.1±3.6	
Educational level								
University	49.5±7.4	0.282	10.8±3.1	0.003	18.7±3.6	<0.001	23.5±3.4	0.146
Other	48.5±6.8		12.2±3.7		20.5±3.6		24.1±3.6	
Non-cancer comorbidities								
Present	48.1±7	0.298	12.6±3	0.016	20±3	0.886	12.6±3.1	0.496
Absent	49±7		11.5±3.7		20±3.9		11.5±3.7	
Psychological support								
Yes	47.6±8	0.215	12.3±3.7	0.329	20.5±4	0.294	24.3±3.5	0.442
No	49±6.8		11.7±3.5		19.9±3.6		23.9±3.5	
Cancer type								
Gastrointestinal	48.9±6.5	0.128	11.5±3.6	0.466	19.8±3.5	0.723	23.8±3.5	0.835
Genitourinary	47.8±7.1		12.4±3.7		20.2±3.7		24.1±3.1	
Breast	50.5±6.8		11.4±3.6		19.6±3.8		24.3±3.6	
Lung	47.4±7.4		11.9±3.2		19.9±3.5		23.6±3.7	
Others	50±7.5		12.2±3.6		20.7±3.9		24.1±3.7	
Cancer stage								
Metastatic	48±6.6	0.060	12.1±3.4	0.176	20.4±3.6	0.036	12.1±3.4	0.495
Non-metastatic	49.6±7.4		11.5±3.7		19.5±3.7		11.5±3.7	

One-way ANOVA was used to compare subscale results based on cancer type, and Student's t-test was used for other comparisons
MAC: Mental Adjustment to Cancer Scale, FS: Fighting spirit, HH: Helplessness/hopelessness, FA: Fatalism, AP: Anxious preoccupation

Discussion

A cancer diagnosis poses a serious threat to patients, extending beyond the physical dimension. It profoundly impacts patients socially, cognitively, and behaviorally. When confronted with a cancer diagnosis and its treatment, patients often experience feelings of fear, loss of control, and uncertainty about the future (23,24). Cancer diagnosis and treatment are frequently accompanied by considerable psychological distress, ranging from anxiety to depression. Studies have reported high prevalence rates of depression (17-36.6%), anxiety (19%) and distress (34.3%) among cancer patients (25-27).

The choice of coping style plays a pivotal role in shaping patients' mood, quality of life, and adherence to treatment. Patients who rely on passive coping strategies such as helplessness/hopelessness, fatalism, or anxious preoccupation experience higher levels of depression, anxiety, and stress, along with a reduced quality of life and lower treatment adherence. In contrast, those who adopt active coping styles such as fighting spirit report lower levels of psychological distress and better quality of life and adherence to treatment (8-14,17,28,29). Given these profound effects, the coping strategies that patients use are of critical importance in cancer care.

Table 4. Regression models examining the relationship between the total B-IPQ score and MAC subscale scores						
Variable	Unstandardized coefficients		Standardized coefficients	t	p-value	Collinearity statistics
	ß	SE	ß			VIF
Model for fighting spirit						
B-IPQ score	-0.209	0.028	-0.409	-7.416	<0.001	1.072
Age ≥65 years	-0.963	0.848	-0.065	-1.135	0.257	1.164
Male sex	-1.714	0.762	-0.122	-2.250	0.025	1.038
Employed	0.879	1.012	0.049	0.868	0.386	1.125
Model for helplessness/hopelessness						
B-IPQ score	0.132	0.013	0.512	9.845	<0.001	1.087
Age ≥65	0.469	0.402	0.063	1.167	0.244	1.162
Employed	-0.362	0.505	-0.040	-0.718	0.473	1.247
University graduation	-0.651	0.420	-0.083	-1.549	0.122	1.159
Metastasis	-0.013	0.366	-0.002	-0.035	0.972	1.060
Model for fatalism						
B-IPQ score	0.064	0.015	0.240	4.142	<0.001	1.060
Employed	-0.345	0.570	-0.037	-0.605	0.546	1.183
University graduation	-1.401	0.487	-0.174	-2.874	0.004	1.158
Metastasis	0.684	0.418	0.093	1.636	0.103	1.028
Model for anxious preoccupation						
B-IPQ score	0.052	0.015	0.204	3.518	0.001	1.000
Male sex	-0.917	0.408	-0.131	-2.246	0.025	1.000

Multivariate linear regression was used to examine the relationship between illness perception and coping strategies
B-IPQ: Brief Illness Perception Questionnaire, MAC: Mental Adjustment to Cancer Scale, SE: Standard error, VIF: Variance inflation factor

Although many studies have examined the relationship between factors such as depression, psychological distress, quality of life, and social support and coping strategies in cancer patients, there is limited research exploring the relationship between illness perceptions and coping strategies in this patient population. Furthermore, the existing studies tend to focus on the relationship between specific subscales of illness perception measures and various coping strategies (30-32). Despite the multidimensional nature of illness perception, patients often form a unified illness perception in their minds. To our knowledge, no study to date investigated the relationship between overall illness perception and coping strategies in cancer patients undergoing chemotherapy. This study is the first to address this gap.

In a study by Rozema et al. (32) involving patients with breast cancer, personal control was found to be positively associated with active coping strategies, while emotional representation was positively associated with passive coping strategies (32). Similarly, in a study including patients with head and neck cancer, Llewellyn et al. (31) reported that identity, timeline, consequences, and emotional representations were positively correlated with passive coping strategies. Furthermore, coherence and personal control had a positive relationship with active coping strategies (31). In another study, Hopman et al. (30) evaluated patients with various types of cancer and determined that timeline, consequences, and emotional representations were positively associated with passive coping strategies, such as helplessness/hopelessness, anxious preoccupation, and fatalism. Additionally, coherence was negatively associated with certain passive coping strategies, specifically anxious preoccupation and fatalism. However, no significant relationship was observed between any illness perception dimensions and active coping strategies (30).

In this study, unlike previous research, we examined the relationship between illness perception and coping strategies using the total B-IPQ score. We found a stronger connection between illness perception and coping strategies than has been identified in prior studies. The effect size of the total B-IPQ score on the fighting spirit and helplessness/hopelessness scores was found to be large, while its effect size on the fatalism and anxious preoccupation scores was small. In contrast to our study, Rozema et al. (32) and Llewellyn et al. (31) did not use a cancer-specific scale, such as the MAC, to evaluate coping strategies. This may have limited their ability to accurately assess the relationship between illness perception and coping strategies. Similar to our study, Hopman et al. (30) demonstrated

a strong relationship between illness perception dimensions and passive coping strategies. However, unlike our findings, they did not observe any significant connection between illness perception dimensions and active coping strategies. It is worth noting that Hopman et al. (30) utilized the revised B-IPQ, where each dimension's influence on coping strategies was analyzed individually. In contrast, we used the total B-IPQ score, which provided a more comprehensive view of the relationship between illness perception and coping strategies. The B-IPQ is simpler, easier to understand, and quicker to complete compared to other scales. This may have led to more accurate responses from patients, allowing us to better uncover the link between illness perception and coping strategies.

Given the significant impact of coping strategies on psychological well-being, quality of life, and treatment adherence, along with the strong association between illness perception and coping strategies, our findings emphasize the importance of incorporating healthcare providers' assessments of patients' illness perceptions into comprehensive cancer care. Targeting negative illness perceptions, especially in patients exhibiting passive coping strategies, could help promote more active coping methods.

Study Limitations

There were some limitations of this study. This study included only cancer patients undergoing chemotherapy, which limited our ability to explore the relationship between illness perception and coping strategies in patients not receiving active treatment. Additionally, the cross-sectional design of the study did not allow for the assessment of the long-term relationship between illness perception and coping strategies.

Conclusion

In conclusion, this study underscores the critical relationship between illness perception and coping strategies, supporting the hypotheses of the common-sense model of self-regulation in cancer patients undergoing chemotherapy. We found that negative illness perceptions were positively associated with passive coping strategies, while they were negatively associated with active coping strategies. These findings highlight the importance of addressing patients' illness perceptions in clinical practice. By targeting and improving negative perceptions, interventions may foster more active coping strategies, which could potentially lead to better psychological well-being, improved quality of life, and greater treatment adherence in cancer care.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ankara University Faculty of Medicine Human Research Ethics Committee (decision no.: İ4-136-19, date: 10.10.2019). All procedures were performed in accordance with ethical standards and the principles of the Declaration of Helsinki.

Informed Consent: Signed informed consent was obtained from all patients before their inclusion in the study.

Footnotes

Authorship Contributions

Concept: Y.Y., F.Ç.Ş., Design: Y.Y., F.Ç.Ş., Data Collection or Processing: Y.Y., M.G., Analysis or Interpretation: Y.Y., M.G., Literature Search: Y.Y., M.G., F.Ç.Ş., Writing: Y.Y., F.Ç.Ş.

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Evaluation of Radiological Abnormalities in Workers Exposed to Heavy Metals and Solvents: A Single-Center Study

Ağır Metal ve Solventlere Maruz Kalan Çalışanlarda Radyolojik Anormalliklerin Değerlendirilmesi: Tek Merkezli Bir Çalışma

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Abstract

Objectives: Heavy metal and solvent exposure is an important occupational hazard that causes serious health problems in industrial workers. This study aimed to evaluate radiological abnormalities in patients diagnosed with occupational heavy metal and solvent toxicity.

Materials and Methods: Retrospectively, 962 male patients between the ages of 18 and 64 who were diagnosed with heavy metal and solvent toxicity between 2018 and 2020 were examined. Radiological evaluations were performed with posterior-anterior chest radiography, high-resolution computed tomography of the thorax, abdominal radiography and abdominal ultrasonography. Abnormal findings were systematically recorded and analyzed.

Results: Emphysema was detected in 29.6% of the patients, hepatosteatosis in 58.1% and osteoporosis in 14.2%. These rates are higher than the rates in the general population. Additionally, 10.2% of patients had a reticulonodular pattern suggestive of pneumoconiosis, while 6.1% had gallbladder polyps.

Conclusion: This study demonstrates severe pulmonary, hepatic, and skeletal abnormalities in workers exposed to heavy metals and solvents. The findings highlight the need for stricter occupational safety regulations, preventive strategies, and regular health screenings for workers at risk. Future studies should focus on prospective studies that include both male and female individuals to understand the long-term effects of these toxic exposures.

Keywords: Occupational exposures, heavy metals, solvents, radiology, fatty liver

Öz

Amaç: Ağır metal ve solvent maruziyeti, endüstriyel çalışanlarda ciddi sağlık sorunlarına yol açan önemli bir mesleki tehlikedir. Bu çalışmada, mesleki ağır metal ve solvent toksisitesi tanısı alan hastalarda radyolojik anormalliklerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Retrospektif olarak 2018-2020 yılları arasında ağır metal ve solvent toksisitesi tanısı alan 18-64 yaş arası 962 erkek hasta incelendi. Radyolojik değerlendirmeler posterior-anterior akciğer grafisi, toraksın yüksek çözünürlüklü bilgisayarlı tomografisi, abdominal radyografi ve abdominal ultrasonografi ile gerçekleştirildi. Anormal bulgular sistematik olarak kaydedildi ve analiz edildi.

Bulgular: Hastaların %29,6'sında amfizem, %58,1'inde hepatosteatoz ve %14,2'sinde osteoporoz tespit edilmiştir. Bu oranlar, genel popülasyondaki oranlarından daha yüksektir. Ek olarak, hastaların %10.2'sinde pnömokonyozu işaret eden retikülonodüler patern saptanmış, %6,1'inde ise safra kesesi polipleri bulunmuştur.

Sonuç: Bu çalışma, ağır metallere ve çözücülere maruz kalan çalışanlarda ciddi pulmoner, hepatik ve iskelet sistemi anormalliklerini ortaya koymaktadır. Bulgular, risk altındaki çalışanlar için daha katı iş güvenliği düzenlemeleri, önleyici stratejiler ve düzenli sağlık taramalarına olan

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ihtiyacı vurgulamaktadır. Gelecekteki çalışmalar, bu toksik maruziyetlerin uzun vadeli etkilerini anlamak için hem erkek hem de kadın bireyleri içeren prospektif araştırmalara odaklanmalıdır.

Anahtar Kelimeler: Mesleki maruziyetler, ağır metaller, solventler, radyoloji, karaciğer yağlanması

Introduction

The rapid development of technology and industrial activities has resulted in a concerning rise in the occurrence of heavy-metal and solvent toxicities, posing significant risks to worker health and safety. Exposure to toxic heavy metals, such as arsenic, cadmium, nickel, mercury, chromium, zinc, lead, and various solvents during industrial processes, such as paint and metal alloy production, can have immediate and long-term health implications (1). Chronic exposure to these substances can result in severe cardiovascular disorders, lung damage, liver damage, peripheral-central neuronal damage, kidney damage, cancer, and diabetes. The toxic effects of heavy metals and solvents are attributed to the production of reactive oxygen species. Chronic heavy metal and solvent toxicity occupational exposure occurs through direct contact, smoke inhalation, and inhalation of aerosols and microparticles. Toxic substances that can be measured in serum in the early stages accumulate in the lungs, kidneys, liver, and central and peripheral nervous systems even after exposure is stopped. The cellular oxidative stress they create here and the important redox enzymes in the oxidative defense mechanism are also affected, adversely affecting cellular energy production and use. Thus, irreversible cell and related organ damage can occur with known apoptosis and necrosis mechanisms. They can cause many disorders such as accelerated atherosclerosis and endothelial damage in the cardiovascular system, damage to alveoli in the lungs, peripheral polyneuropathies, neurodegenerative changes in the central nervous system, tubular necrosis in the kidneys, fatty liver, steatohepatitis, cirrhosis, and hepatocellular cancer (2-9). Exposure to heavy metals and solvents during industrial processes can lead to serious health complications. Despite the known risks, limited research focuses on the radiological manifestations of these toxic exposures. Therefore, this study aims to systematically evaluate radiological abnormalities in affected patients.

Materials and Methods

This study was conducted retrospectively and received approval from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Keçiören Training and Research Hospital. from the ethics committee (decision no.: 2012-KAEK-15/2264, date: 23.03.2021) We enlisted the participants who made reference to our institution within 2018 and 2020.

Participants

Patients received outpatient examinations or inpatient diagnosis and treatment at our institution.

The Inclusion Criteria

a) Being aged between 18 and 64

b) Diagnosed with occupational heavy metal or solvent toxicity

The Exclusion Criteria

a) Being under the age of 18 or over the age of 65

b) Patients with missing radiological examinations

Data Sources

Demographic, clinical, and occupational information collected during the research population's hospital admissions, laboratory, and radiology examinations was retrospectively assessed. Radiology records were reviewed for patients with heavy metal or solvent poisoning. The records included posterior-anterior chest X-rays, thorax high-resolution computed tomography (HRCT), direct abdominal radiography, and abdominal ultrasonography. Abnormal radiological findings were recorded. All patients underwent clinical and radiological evaluations to exclude alternative diagnoses, including active or past tuberculosis, interstitial lung disease, and rheumatologic conditions, before attributing findings to occupational heavy metal exposure.

Statistical Analysis

The statistical analysis was conducted using SPSS version 22.0. Continuous variables were represented using the mean value plus or minus the standard deviation, while categorical variables were presented as counts and percentages.

Results

The data of 984 patients admitted with occupational heavy metal and solvent poisoning were evaluated retrospectively. Of the 984 patients, 962 met the study inclusion criteria. Twenty-two patients were excluded from the study due to incomplete radiological examinations. The flowchart is shown in Figure 1.

All the patients were male. The average age is 379± years. Of the 962 patients, 961 (99.8%) were present with lead, 75 (7.8%) with solvent, 625 (64.9%) with manganese, 230 (23.9%) with cadmium, 9 (1%) with chromium, 78 (8.1%) with nickel, 80 (8.3%) with arsenic, 21 (2.2%) with mercury, 73 (7.6%) with

antimony, 31 (3.2%) with molybdenum, 21 (2.2%) with cobalt, 7 (0.7%) with polyaromatic hydrocarbon, 2 (0.2%) with thallium and 7 (0.7%) with zinc.

Smoking was reported in 65.3% (n=628) of patients, and alcohol consumption in 24.5% (n=236). Occupational distribution indicated that 48.5% (n=466) of the patients worked in battery production and recycling facilities, 28.6% (n=275) in ore mining operations, and 22.9% (n=221) in other industries, including paint and metal processing. Patients with comorbidities included 18.6% (n=179) with diabetes and 12.9% (n=124) with hypertension. No history of active or past tuberculosis, nor significant rheumatologic or pulmonary diseases, was identified in the cohort.

Exposure duration varied across the study population. A larger proportion of patients (54.2%, n=521) had been exposed for less than 5 years, 33.6% (n=323) for 5-10 years, and 12.2% (n=118) for more than 10 years.

Morbidity due to occupational heavy metal or solvent exposure and radiological findings of these patients are shown in Table 1. Morbidities such as pneumoconiosis, osteoporosis and hepatosteatosis diagnosed in this study population were derived from clinical notes of hospital-affiliated multidisciplinary occupational diseases health board as being due to chronic occupational exposure to heavy metals and solvents. Pneumoconiosis and osteoporosis were identified in 108 (11.2%) and 136 (14.2%) individuals, respectively. The average age of patients with osteoporosis was 32.5±10.2 years. The most prevalent abnormalities on abdominal ultrasonography were hepatomegaly (254, 26.4%), hepatosteatosis (560, 58.1%), and gallbladder polyps (58, 6.1%).

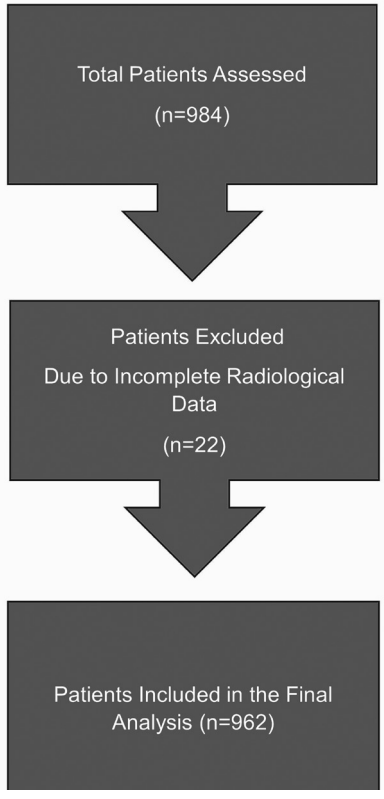

Figure 1: The flowchart of the study

Discussion

Our study examines radiological anomalies in patients with occupational heavy metal and solvent toxicity, revealing some differences from findings in the general population. It emphasizes the effects of persistent exposure to toxicants on several organ systems, particularly the respiratory and hepatic systems.

Clinically, 11.2% of the study population had a diagnosis of pneumoconiosis. Chest X-ray findings revealed a reticulonodular pattern in 10.2% of patients, while HRCT identified pulmonary nodules in only 1.1% of cases. This highlights a significant discrepancy. The relatively high prevalence of reticulonodular patterns observed on chest X-rays may be attributed to the low specificity of this imaging modality, as it can detect non-specific changes that are not necessarily related to pneumoconiosis or occupational exposure. Furthermore, the absence of comprehensive studies evaluating the prevalence of reticulonodular patterns in the general population adds to the complexity of interpreting these findings. This limitation makes it challenging to definitively attribute these patterns to occupational exposure. Future studies incorporating HRCT and larger control groups are necessary to improve our understanding of the diagnostic accuracy and specificity of these imaging modalities in the context of occupational lung diseases (10).

HRCT findings, such as apical fibrosis, were evaluated alongside patients' clinical histories. The absence of active or past tuberculosis, interstitial lung disease, or other significant pulmonary conditions was confirmed during the diagnostic process, supporting the attribution of findings and comorbidities to occupational heavy metal exposure. HRCT scans provided further information on lung findings. While emphysema was observed in 29.6% of the study population, determining whether this finding is predominantly attributable to occupational heavy metal exposure or smoking is challenging. The high smoking rate among participants (65.3%) suggests that both factors may have contributed, acting either independently or synergistically. Future studies with detailed exposure assessments and smoking-independent control groups are needed to clarify the primary drivers of emphysema in this population.

Radiology plays a crucial role in diagnosing pulmonary pathologies in workers exposed to heavy metals and solvents, as these exposures can lead to various occupational lung

diseases. The imaging features of these diseases are often complex and require a comprehensive understanding of the patient's occupational history and exposure details to interpret radiographic accurately and CT findings (11,12). HRCT is particularly effective in identifying parenchymal, airway, and pleural abnormalities associated with these conditions, surpassing traditional chest radiography in diagnostic accuracy (13). Exposure to heavy metals such as cadmium, manganese, and nickel can result in acute conditions like chemical pneumonitis and pulmonary edema, as well as chronic diseases

Table 1: Morbidity due to occupational heavy metal or solvent exposure and radiological findings of the patients*

		n, (%)
Morbidities	Cerebrovascular disease	2 (0.2)
	Hypertrophic cardiomyopathy	9 (1.0)
	Pneumoconiosis	108 (11.2)
	Osteoporosis	136 (14.2)
Chest X-ray findings	Reticulonodular pattern	98 (10.2)
	Solitary nodule	24 (2.5)
	Cardiothoracic index >0.5	12 (1.3)
	Pericardial fat pad	22 (2.3)
	Prominent aortic knob	47 (4.9)
	Hilar enlargement	3 (0.3)
	Elevated diaphragm	4 (0.5)
Abdomen X-ray findings	Phlebolith	6 (0.6)
HRCT findings	Fibrosis	14 (1.5)
	Apical fibrosis	21 (2.2)
	Vascular variations	3 (0.3)
	Nodule	11 (1.1)
	Respiratory bronchiolitis	42 (4.3)
	Bronchial wall thickening	30 (3.1)
	Mucus impaction	18 (1.8)
	Atelectasis	14 (1.5)
	Vertebral degeneration	264 (27.4)
	Cardiomegaly	69 (7.2)
	Aortic atherosclerosis	3 (0.3)
	Emphysema	285 (29.6)
	Diaphragm elevation	8 (0.8)
Abdominal US findings	Hepatomegaly	254 (26.4)
	Hepatosteatosis	560 (58.1)
	Area separated by fat	22 (2.3)
	Gallstone	10 (0.1)
	Gallbladder polyp	58 (6.1)
	Splenomegaly	15 (1.6)
	Accessory spleen	11 (1.1)
	Kidney stone	40 (4.1)
	Renal cyst	31 (3.2)
	Increased renal parenchyma echogenicity	8 (0.8)
	Hydronephrosis	7 (0.7)
	Pyelonephritis sequela	9 (0.9)

*An individual may present with more than one morbidity or finding
HRCT: High-resolution computed tomography, US: Ultrasound

such as emphysema and pulmonary fibrosis (14). For instance, cadmium exposure is linked to emphysema, while cobalt exposure can lead to hard metal lung disease characterized by interstitial pneumonitis. Additionally, certain metals like arsenic, chromium, and nickel are recognized lung carcinogens, contributing to a significant proportion of occupational lung cancer cases (14). The accurate diagnosis of these conditions is critical, as misdiagnosis can lead to irreversible health outcomes, underscoring the importance of radiologists and clinicians being adept at recognizing both common and uncommon imaging features of occupational lung diseases (11).

Abdominal ultrasonography revealed a high prevalence of hepatosteatosis (58.1%) in the study population, which significantly exceeded the prevalence reported in the general population, which ranges from 20% to 30% depending on risk factors such as obesity and diabetes (15). This high prevalence in our study population highlights the hepatotoxic potential of heavy metals and solvents, as the liver is the primary detoxification organ exposed to these toxins (15). This high prevalence in our study population highlights the hepatotoxic potential of heavy metals and solvents, as the liver is the primary detoxification organ exposed to these toxins. Chronic exposure to heavy metals can disrupt lipid metabolism and promote oxidative stress, leading to fat accumulation in hepatic cells (16).

Gallbladder polyps were detected in 6.1% of patients, a remarkable finding considering their relatively low prevalence in the general population (17). In the context of heavy metal and solvent exposure, the formation of gallbladder polyps may be related to chronic inflammation and cellular proliferation driven by toxic insults to the biliary epithelium. These processes may lead to the development of benign neoplastic growths. Follow-up, perhaps over many years, is needed to understand the proportion of these polyps progressing to malignancy. Figure 2 displays an ultrasonographic image of numerous polyps in the gallbladder of a patient who has lead poisoning.

Exposure to heavy metals and solvents has been linked to an increased risk of osteoporosis, as evidenced by multiple studies. Heavy metals such as cadmium and lead have been shown to negatively impact bone mineral density (BMD), contributing to conditions like osteopenia and osteoporosis. A systematic review and meta-analysis found that cadmium exposure significantly increased the risk of these conditions, particularly in older adults and men, while lead exposure was more pronounced in men (18). Additionally, a study using data from the National Health and Nutritional Examination Surveys highlighted a strong positive relationship between blood cadmium levels and the prevalence of osteoporosis (19). The molecular mechanisms underlying these effects involve the deregulation of detoxifying enzymes, as seen in osteoporotic patients with elevated plasma levels of heavy metals like copper and lead, which correlate with altered gene expression patterns (20). Furthermore, environmental pollutants, including heavy metals and solvents, have been identified as modifiable risk factors for osteoporosis, emphasizing the need for improved environmental policies to mitigate these risks (21). The prevalence of osteoporosis (14.2%) in this relatively young cohort (mean age 32.5 years) is of particular concern. Osteoporosis is commonly seen in older adults and postmenopausal women, but in our study it appears to be directly linked to toxic exposure. Heavy metals such as lead and cadmium can interfere with bone metabolism by disrupting calcium homeostasis and promoting osteoclast activity while inhibiting osteoblast function (22). It may result in decreased BMD and increased fracture risk, as evidenced by the high incidence of osteoporosis among exposed workers.

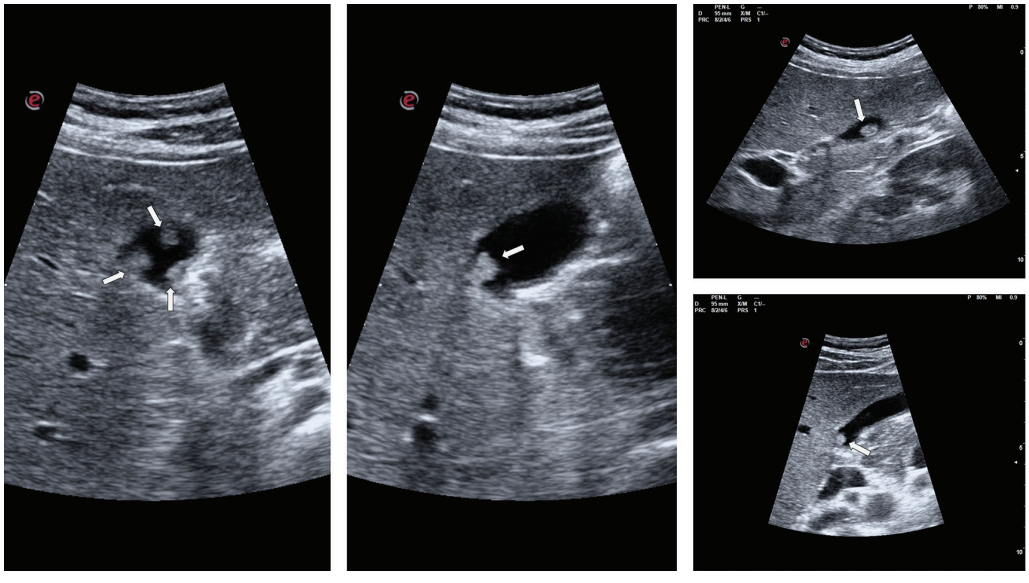

Figure 2: Ultrasound images of gallbladder polyps. These images show polyps in the lumen of the gallbladder in different lead-exposed workers (arrows)

A notable aspect of our study is that all patients were male. This gender homogeneity likely reflects the workforce's demographic makeup in traditionally male-dominated industries with high exposure to heavy metals and solvents. However, this introduces a potential bias and limits the generalizability of our findings to female workers, who may experience different health effects from similar exposures. Women may have different physiological responses to toxic exposures, influenced by factors such as hormonal differences and changing body fat composition that may affect the distribution and storage of toxicants. Future research should aim to include female workers to provide a more comprehensive understanding of occupational health risks associated with heavy metal and solvent exposure.

Study Limitations

The study had several limitations. The study's retrospective nature may have introduced biases regarding the completeness and accuracy of the recorded data. Some relevant clinical or exposure details may not have been adequately documented. Furthermore, the fact that the study was conducted at a single center may limit the generalizability of the findings to other populations or geographic areas. The study did not provide longitudinal follow-up, which would have been valuable in understanding the progression and long-term outcomes of the identified radiological abnormalities.

Conclusion

In conclusion, our study demonstrates significant radiological abnormalities among workers exposed to heavy metals and solvents, revealing substantial impacts on pulmonary, hepatic, and skeletal systems. These findings emphasize the critical need for targeted preventive strategies and comprehensive occupational health measures to protect workers in high-risk industries. The observed abnormalities underline the importance of early detection and systematic health evaluations to mitigate the health consequences of prolonged toxic exposures. The study's retrospective design, single-center focus, and lack of longitudinal follow-up are notable limitations that may affect the generalizability and depth of the findings. Future research should prioritize prospective, multi-center studies with diverse populations, including both male and female workers, to provide a more nuanced understanding of these exposures' effects. Additionally, integrating long-term follow-up and well-matched control groups will be essential to delineate the direct impacts of occupational exposure from other contributing factors.

Ethics

Ethics Committee Approval: This study was conducted retrospectively and received approval from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Keçiören Training and Research Hospital (decision no.: 2012-KAEK-15/2264, date: 23.03.2021).

Informed Consent: Informed consent was not obtained since it was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practies: H.B., A.S., Concept: H.B., L.C.A., Ö.A., A.S., Design: H.B., L.C.A., Ö.A., Data Collection and Processing: H.B., L.C.A., A.S., Analysis or Interpretation: H.B., L.C.A., Literature Search: H.B., Ö.A., A.S., Writing: H.B.

Conflict of Interest: According to the authors, there are no conflicts of interest related to this study.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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DAHİLİ TIP BİLİMLERİ / MEDICAL SCIENCES

Diyabetik Hastalarda DPP-4 İnhibitörleri Kullanımının Gastroparezik Semptomlar Üzerine Etkisi

Impact of DPP-4 Inhibitors on Gastroparesis Symptoms in Patients with Diabetes Mellitus

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Öz

Amaç: Çalışmada tip 2 diabetes mellitus (T2DM) tanısı ile dipeptidil peptidaz 4 enzim inhibitörleri (DPP-4-İ) kullanan hastalarda, DPP-4-İ'nin diyabetik gastroparezi semptomları üzerine etkilerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Şubat 2022-Temmuz 2022 tarihleri aralığında Ankara Üniversitesi Tıp Fakültesi, Endokrinoloji Kliniği'nde T2DM tanısı ile takip edilen 203 hasta çalışmaya alındı. Tüm hastalarda gastroparezi semptomları sorgulaması; Gastroparezi Ana Semptom İndeksi (GCSI) anketine göre değerlendirildi.

Bulgular: Çalışmamızda toplam 203 hasta değerlendirilmiş olup hastaların 114'ü (%56,2) kadın, 89'u (%43,8) erkekti ve ortanca [çeyrekler aralığı (ÇA)] hemoglobin A1c (HbA1c) düzeyleri 7,9 (3), ortanca (ÇA) diyabetli hastalık süreleri 12 (14) yıl olarak tespit edildi. Hastalarımızda gastroparezi semptomları sorgulamasına yönelik yapılan GCSI anketine göre alt gruplar içinde bulantı-kusma bölümü (p=0,50), şişkinlik bölümü (p=0,24) ve ortalama total skor (p=0,14) olup sonuçların her iki grupta benzer olduğu saptandı. Ancak erken doyma/postprandial tokluk hissi bölümü sorgulandığında DPP-4-İ kullanan diyabetik hasta grubunda gastroparezi semptom skorunun daha düşük olduğu bulundu (p=0,048). Kullanılan DPP-4-İ grubu ilaçlar arasında da gastroparezi semptom skoru açısından bir fark bulunmamıştır (p=0,50).

Sonuç: Diyabetik hastalarda düşünülenin aksine, DPP-4-İ'nin kullanımı sonrası erken doyma/postprandial tokluk hissi bölümünde gastroparezi semptom skoru daha düşük saptanmıştır. Ancak yaş, hastalık süresi, HbA1c gibi değerler ile GCSI skorları arasında anlamlı bir korelasyon bulunmamıştır.

Anahtar Kelimeler: Diabetes mellitus, DPP-4 enzim inhibitörleri, gastroparezi

Abstract

Objectives: This study aimed to investigate potential effects of dipeptidyl peptidase 4 enzyme inhibitors (DPP-4-I) on gastroparesis symptoms in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: The study sample consisted of 203 patients with T2DM followed up between February and July 2022 at the Endocrinology Clinic of Ankara University Faculty of Medicine. Gastroparesis symptoms were assessed in all patients through the Gastroparesis Cardinal Symptom Index (GCSI).

Results: A total of 203 patients were evaluated in our study, 114 (56.2%) of the patients were women, 89 (43.8%) were men, and the median [interquartile range (IQR)] hemoglobin A1c (HbA1c) levels were 7.9 (3), and the median (IQR) diabetes disease duration was determined as 12 (14) years. According to the GCSI questionnaire conducted to question the symptoms of gastroparesis in our patients, the nausea/vomiting section (p=0.50), bloating section (p=0.24), and mean total score (p=0.14) were found to be similar in both groups. However, when the feeling of early satiety/postprandial fullness was questioned, it was observed that the gastroparesis symptom score was lower in the diabetic patient group using DPP-4-I (p=0.048). No significant difference in gastroparesis scores was observed between different DPP-4-I medications (p=0.50).

Conclusion: Contrary to expectations, Contrary to expectations, gastroparesis symptom scores were found to be lower in the early satiety/postprandial fullness section after the use of DPP-4-I. However, there was no significant correlation between age, disease duration, HbA1c, and GCSI.

Keywords: Diabetes mellitus, DPP-4 enzyme inhibitors, gastroparesis

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Giriş

Mekanik obstrüksiyon varlığı dışlanan olgularda; gecikmiş mide boşalması ile karakterize anormal gastroduodenal motilite bozukluğu gastroparezi olarak adlandırılmaktadır (1). Dünyada gastroparezi prevalansı net olarak bilinmemekle birlikte, son dönemde Avrupa'da yapılan bir epidemiyolojik çalışmada, gastroparezinin tahmini genel prevalansı 100.000 kişide 13,8, görülme sıklığı ise 100.000 kişi yılı başına 1,9 olarak bulunmuştur (2). Etiyolojide olguların çoğunluğu idiopatik, iatrojenik ve geçirilmiş cerrahilere bağlı görülmekle birlikte, sistemik hastalıklardan en sık diabetes mellitus (DM), suçlanmaktadır (1). Tip 1 DM (T1DM) ve T2DM hastalarında tahmini 10 yıllık kümülatif gastroparezi insidansının sırasıyla %5,2 ve %1 olduğu tahmin edilmektedir (3). Diyabetik gastroparezide başlangıç döneminde semptomlar hafif seyrederken, ileri dönemlerde semptomlar şiddetlenir. Diyabetik hastalarda bulantı, kusma, iştahsızlık, erken doyma, midede dolgunluk hissi ve karın ağrısı, yemek sonrası olan hazımsızlık gibi semptomların varlığında mutlaka gastroparezi akla gelmelidir. Semptom şiddeti ve hastalığa özgü sağlıkla ilgili yaşam kalitesi sonuçları, gastrointestinal bozukluklara yönelik tedavilerin etkinliğinin değerlendirilmesi için önemlidir. Gastroparezi için klinik testler tanı için faydalı olsa da daha invaziv oldukları, zaman alıcı oldukları ve her zaman hasta semptom raporlarıyla yakından ilişkili olmayabilecekleri için tedavi sonuçlarının değerlendirilmesinde sınırlı değere sahiptirler. Buna çözüm olarak; bulantı-kusma, erken doyma/postprandial tokluk hissi ve şişkinlik olmak üzere üç alt ölçekten oluşan klinisyenler tarafından kullanılabilecek noninvaziv bir yöntem olan Gastroparezi Ana Semptom İndeksi (GCSI) geliştirilmiştir (4). Klinik pratikte hastalar GCSI anketi ile değerlendirildiğinde gastroparezi semptom şiddeti ile GCSI toplam puanı arasında anlamlı ilişkiler gözlenmiştir ve GCSI güvenilir ve işlevli bir ölçüm metodu olarak kabul edilmiştir (4). Ülkemizde de klinik araştırmalar için GCSI anketi daha önce kullanılmıştır (5).

İnsülin direnci ile birlikte kısmi insülin eksikliği ile seyredebilen T2DM'de önemli defektlerden birisi de gastrointestinal sistem kaynaklı inkretin hormonların düzeyi veya etkisinin azalmasıdır. İnkretin hormonların etkisini artırmaya yönelik ilaçlar; endojen inkretinlerin yemek sonrası yıkımını, DPP-4 enzimini inhibe etmek suretiyle geciktirerek endojen glukagon benzeri peptid-1 (GLP-1) ve gastrik inhibitör peptid düzeylerini yükseltir, insülin sekresyonunu glukoza bağımlı olarak artırır, alındıktan sonraki postprandiyal glukoz düzeyini ılımlı miktarda düşürür ve glukagon sekresyonunu baskılarlar (6). GLP-1 midedeki reseptörleri aracılığı ile mide boşalma zamanında gecikmeye ve gastrik asit sekresyonunda azalmaya yol açar. GLP-1 reseptörü üzerinden etki eden reseptör agonistleri de, GLP-1 reseptörlerini aktive ederek pankreas beta hücrelerinin glukoza duyarlılığını artırır, alfa hücrelerinden glukagon sekresyonunu baskılar, gastrik boşalmayı geciktirir ve doyma hissini artırırlar (7). DPP-4 inhibitörleri, insülinin uyarılması ve glukagon salgısının inhibisyonu dahil olmak üzere GLP-1 reseptör agonistlerine atfedilen eylemlerin çoğunu taklit eder (8). Buna rağmen GLP-1 RA'ların gastrik boşaltmayı yavaşlattığı bilinse de DPP-4-İ'leri, bu durumla kesin olarak ilişkilendirilememiştir (8). DPP-4-İ'nin yemek sonrası glisemide azalmaya aracılık ettiğine dair öne sürülen mekanizmalar hakkında ve özellikle de DPP-4-İ'nin mide boşalmasını yavaşlatma kapasitesine sahip olup olmadığı konusundaki etkileri hala tam olarak bilinmemektedir.

Çalışmamızda; diyabetik hastalarda gastroparezi semptomlarına yönelik sorgulamada GCSI anketi kullanılarak semptomların varlığı ve şiddetinin belirlenmesi ve özellikle DPP-4-İ'yi kullanan hastalarda, DPP-4-İ'nin diyabetik gastroparezi semptomları üzerine etkilerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem

Şubat 2022-Temmuz 2022 tarihleri aralığında Ankara Üniversitesi Tıp Fakültesi, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı'nda T2DM tanısı ile takip edilen ve oral antidiyabetiklerden DDP4-İ tedavisi alan 102 hasta ile DPP-4-İ tedavisi almayan 101 hasta olmak üzere toplam 203 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik bulguları, eşlik eden hastalıklar, DM'ye bağlı mikrovasküler-makrovasküler komplikasyonlar, açlık kan glukozu, tokluk kan glukozu, hemoglobin A1c (HbA1c) ve diğer laboratuvar bulguları kaydedildi. On sekiz yaşın altındaki hastalar çalışmaya alınmadı. Gastroözefageal reflü hastalığı, enflamatuvar barsak hastalığı, bağ dokusu hastalığı, malignite tanısı olanlar ve geçirilmiş obezite cerrahisi öyküsü gibi gastrik motiliteyi etkileyecek eşlik eden hastalığı olanlarda çalışmaya dahil edilmedi. Ayrıca DPP-4-İ tedavisi almayan gruptaki hastalar içerisinde GLP-1 reseptör agonisti kullanan hastalarda çalışmaya dahil edilmemiştir.

Tüm hastalarda gastroparezi semptomları sorgulaması; GCSI anketine göre değerlendirildi (4). GCSI bulantı-kusma, erken doyma/postprandial tokluk hissi ve şişkinlik olmak üzere üç alt ölçekten oluşmaktadır. Üç alt ölçeğin ortalaması alınarak total skor elde edilmiştir. GCSI anketi daha önce ülkemizde de klinik araştırmalar için kullanılmıştır (5).

Çalışma için Ankara Üniversitesi Tıp Fakültesi Klinik Araştırmalar ve Etik Kurulu'ndan onay alınmıştır (tarih: 16.02.2022, karar no: İ02-86-22). Tüm hastalardan çalışma hakkında onam alınmıştır.

İstatistiksel Analiz

Verilerin analizi Statistical Package for Social Sciences version (IBM SPSS) 25 paket programı kullanılarak yapıldı.

Değişkenlerin normal dağılıma uygunluğu görsel (histogram ve olasılık grafikleri) ve analitik yöntemlerle (Kolmogorov-Smirnov/Shapiro-Wilk testleri) incelendi. Tanımlayıcı analizler normal dağılan sayısal değişkenler için ortalama ve standart sapma; normal dağılmayan sayısal değişkenler için ortanca ve çeyrekler arası aralık; ordinal ve kategorik değişkenler için ise frekans tabloları ile verildi. Gruplar arası karşılaştırmalarda, sayısal değişkenler için Mann-Whitney U testi, kategorik değişkenler için ise yerine göre ki-kare ya da Fisher testi kullanıldı. İkiden fazla grupta, değişkenler arasında fark saptandığında, farkın kaynaklandığı grubun tespiti için Bonferroni düzeltmesi ile ikili karşılaştırmalar yapıldı. Spearman testi kullanılarak değişkenler arasında korelasyon analizi yapıldı. P<0,05 için sonuçlar istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmamızda toplam 203 hasta değerlendirilmiş olup hastaların 114'ü (%56,2) kadın, 89'u (%43,8) erkekti ve ortanca [çeyrekler aralığı (ÇA)] HbA1c düzeyleri 7,9 (3), ortanca (ÇA) diyabet tanı süreleri 12 (14) yıl olarak tespit edildi. Hastalarda ortanca (ÇA) yaş 62 (17) ve ortanca (ÇA) VKİ 29,5 (8,9) kg/m^2 olarak saptandı. Çalışmaya dahil edilen hastalardan; T2DM tanısı ile takip edilen ve tedavi de DPP-4-İ tedavisi almayanlar; grup-1, DPP-4-İ tedavisi alan hastalar ise grup 2 olarak adlandırıldı. Her iki grupta HbA1c değerleri incelendiğinde; DPP-4-İ$^-$ hastalarda ortanca (ÇA) HbA1c düzeyleri 7,8 (3,3), DPP-4-İ$^+$ grupta ise ortanca (ÇA) HbA1c düzeyi 8,01 (2,9) olarak tespit edildi (p=0,101). Tüm hastaların demografik özellikleri ve laboratuvar bulguları Tablo 1'de özetlenmiştir.

Çalışmamızda DPP-4-İ$^-$ ve DPP-4-İ$^+$ olan her iki grupta mikrovasküler ve makrovasküler komplikasyonlara yönelik yapılan incelemede istatistiksel olarak anlamlı düzeyde farklılık saptanmadı. Kullanılan oral antidiyabetik tedavilere bakıldığında metformin kullanımı ve metformin + sodyum glukoz ko-transporter 2 inhibitörleri (SGLT-2-İ) kombinasyonu kullanımı dağılımının her iki grupta benzer olduğu görüldü. Ayrıca grup 1'de (DPP-4-İ$^-$) insülin tedavisi kullanımı %55,4, grup 2'de (DPP-4-İ$^+$) ise %67,6 olarak tespit edildi (p=0,074). Tüm hastaların klinik bulguları ve kullanılan tedavilerin karşılaştırılması Tablo 2'de özetlenmiştir.

Hastalarımızda gastroparezi semptomları sorgulamasına yönelik yapılan GCSI anketi sonuçları kıyaslandığında; anketin alt grupları içinde bulantı-kusma bölümü (p=0,50), şişkinlik bölümü (p=0,24) ve ortalama total skor (p=0,14) sonuçlarının her iki grupta benzer olduğu ve istatistiksel olarak anlamlı farklılık olmadığı saptandı. Ancak erken doyma/postprandial tokluk hissi bölümüne bakıldığında DPP-4-İ kullanan diyabetik hasta grubunda gastroparezi semptom skorunun anlamlı düzeyde daha düşük olduğu görüldü (p=0,048) (Tablo 3).

Her iki grupta yer alan hastalarda yaş, diyabet hastalık süresi, VKİ, açlık kan şekeri, tokluk kan şekeri ve HbA1c ile GCSI anketi alt bölümleri arasında yapılan sperman korelasyon analizi sonuçları Tablo 4'te verilmiştir. Çalışmamızda diyabetik hasta grubunda DPP-4-İ kullanımı açısından ayrıntılı incelendiğinde 43 hasta sitagliptin, 39 hasta vildagliptin ve 20 hasta linagliptin tedavisi alıyordu. Kullanılan DPP-4-İ ilaçlar arasında da GCSI anketi sonuçları açısından anlamlı bir fark bulunmadı (p=0,50).

Tartışma

DM, gastroparezi ile ilişkili en sık suçlanan sistemik hastalıktır. Diyabetik gastroparezinin patogenezi çok yönlüdür ve otonom nöropati zemininde proksimal mide, antrum, pilor ile duodenumu içeren heterojen motor fonksiyon bozuklukları ve midenin bu farklı bölgeleri arasındaki motor aktivite koordinasyonunun bozulması ile ilişkilendirilmiştir (9). Diyabetli hastalarda popülasyona dayalı yapılan çalışmalarda, hastaların %11 ila 18'inde üst gastrointestinal semptomların olduğu bildirilmiştir ve bunların çoğu gecikmiş mide boşalmasıyla ilişkilidir (10-13). Uzun süreli T2DM'lilerde mide boşalmasında gecikme %30 civarında tespit edilmiştir (10). Kan şekeri konsantrasyonundaki akut değişikliklerin de, hem sağlıklı hem de diyabetik kişilerde mide boşalması üzerinde büyük bir etkiye

Tablo 1: Tüm hastaların demografik özellikleri ve laboratuvar bulguları

	Tüm hastalar, n: 203 (%)
Cinsiyet, (%)	
Kadın	114 (56,2)
Erkek	89 (43,8)
Yaş, yıl, ortanca (ÇA)	62 (17)
VKİ, kg/m^2, ortanca (ÇA)	29,5 (8,9)
Açlık kan glukozu (mg/dL) ortanca (ÇA)	128 (52)
Tokluk kan glukozu (mg/dL) ortanca (ÇA)	182 (85)
HbA1c (%), ortanca (ÇA)	7,9 (3)
ALT U/L, ortanca (ÇA)	19 (12)
AST U/L, ortanca (ÇA)	18 (8)
BUN mg/dL, ortanca (ÇA)	16 (9)
Kreatinin (mg/dL) ortanca (ÇA)	0,82 (0,35)
Sodyum (Na) mg/dL ortanca (ÇA)	139 (3)
Potasyum (K) mg/dL, ortanca (ÇA)	4,5 (0,5)
Kalsiyum (Ca) mg/dL, ortanca (ÇA)	9,5 (0,5)
Fosfor (P) mg/dL, ortalama ± SS	3,8 (0,9)
Trigliserit mg/dL, ortanca (ÇA)	163 (102)
Total kolesterol mg/dL, ortanca (ÇA)	173,2 (60)
LDL kolesterol mg/dL, ortalama ± SS	94,4±35,1
HDL kolesterol mg/dL, ortanca (ÇA)	43 (17)

ÇA: Çeyrekler aralığı, SS: Standart sapma, VKİ: Vücut kütle İndeksi

sahip olduğu ve özellikle belirgin hiperglisemininin katı ve sıvıların mide boşalmasını önemli ölçüde yavaşlattığı kabul edilmektedir (14,15). Literatürde kadınlarda, erkeklere göre gastroparezinin 4 kat daha fazla olduğu ve tipik olarak en az on yıldır diyabet tanısı olan hastalarda ortaya çıktığı, dolayısıyla T2DM'li yaşlı bireylerde daha sık görüldüğü düşünülmektedir (16,17). Yüksek HbA1c düzeyleri ve diyabetin mikrovasküler ve makrovasküler komplikasyonlarının gelişmiş olması da diyabetik gastroparezi için risk faktörleri olarak kabul edilmektedir. Her ne kadar akut hiperglisemininin, mide boşalması üzerinde tipik olarak geri dönüşümlü bir etkiye sahip olduğu kabul edilse de, kötü kontrollü diyabetik hastalardaki kronik hiperglisemi, artan nöropati riskiyle ilişkilidir. Çalışmamızda T2DM nedeniyle takip edilen hastalarda ortanca (ÇA) yaş 62 (17) iken, hastaların 114'ü (%56,2) kadın, 89'u (%43,8) erkekti ve diyabet hastalığı süresi ortanca (ÇA) 12 (14) yıl olup, ortanca (ÇA) HbA1c düzeyleri ise %7,9 (3), idi. Mikrovasküler komplikasyonların varlığı değerlendirildiğinde; tüm hastaların %43,3'ünde periferik nöropati, %37,9'unda retinopati, %21,1'inde ise diyabetik böbrek hastalığı eşlik etmekteydi. Ayrıca kan şeker profiline bakıldığında; ortanca (ÇA) açlık kan glukozu düzeyi 128 (52) mg/dL ve ortanca (ÇA) postprandial kan glukozu 182 (85) mg/dL olarak tespit edildi.

Tablo 2: T2DM'li hasta grubunda klinik bulgular ve uygulanan tedavilerin karşılaştırılması

	Grup 1, DM+, DPP-4-İ- n=101	Grup 2, DM+, DPP-4-İ+, n=102	p-değeri
DM hastalık süresi, yıl, ortanca (ÇA)	12 (16)	13,5 (13)	0,14[b]
HbA1c (%), ortanca (ÇA)	7,8 (3,3)	8,01 (2,9)	0,10[b]
VKİ, kg/m^2, ortanca (ÇA)	29,9 (11)	29,1 (7,7)	0,35[b]
En sık eşlik eden hastalıklar			
Primer hipertansiyon, (%)	74 (73,3)	84 (82,4)	0,12[a]
Hiperlipidemi, (%)	61 (60,4)	72 (70,6)	0,13[a]
Primer hipotiroidi, (%)	18 (17,8)	17 (16,7)	0,83[a]
Eşlik mikrovasküler komplikasyonlar			
Diyabetik nöropati, (%)	42 (41,6)	46 (45,1)	0,61[a]
Diyabetik retinopati, (%)	37 (36,6)	40 (39,2)	0,71[a]
Diyabetik böbrek hastalığı, (%)	19 (18,8)	24 (23,5)	0,41[a]
Eşlik eden makrovasküler komplikasyonlar			
Aterosklerotik kalp hastalığı, (%)	37 (36,6)	41 (40,2)	0,60[a]
Periferik arter hastalığı, (%)	4 (4)	6 (5,9)	0,75[c]
Serebrovasküler olay, (%)	3 (3)	4 (3,9)	>0,99[c]
Oral antidiyabetikler			
Metformin, (%)	91 (90,1)	88 (86,3)	0,40[a]
Metformin + SGLT2-İ kombinasyonu, (%)	39 (38,6)	37 (36,3)	0,73[a]
İnsülin tedavisi, (%)	56 (55,4)	69 (67,6)	0,074[a]

+Ortanca (ÇA: Çeyrekler aralığı), [a]Chi-Square, [b]Mann-Whitney U, [c]Fisher's Exact test. P<0,05 için sonuçlar istatistiksel olarak anlamlı kabul edildi
n (%): Sayı (yüzde), T2DM: Tip 2 diabetes mellitus, DPP-4-İ: Dipeptidil peptidaz 4 enzim inhibitörleri, SGLT2-İ: Sodyum glukoz ko-transporter 2 inhibitörleri, VKİ: Vücut kütle indeksi

Diyabetik hastalarda mide bulantısı, kusma, erken doyma, yemek sonrası dolgunluk, karın ağrısı veya şişkinlik şikayeti olması halinde gastroparezideن şüphelenilmelidir. Mekanik obstrüksiyonu ve diğer gastroparezi sebeplerini ekarte etmek için gastroskopi ve gereklilik halinde mutlaka abdomen bilgisayarlı tomografi (BT), manyetik rezonans görüntüleme gibi ek görüntülüme yöntemleri ile değerlendirilmelidir. Ancak diyabetik gastroparezi kesin tanısı; uygun maliyetli, yaygın olarak kullanılan invaziv olmayan ve altın standart olarak kabul edilen sintigrafi yöntemi ile mide boşalmasının ölçülmesi ile konulur. Bunun yanında gastrik boşalmayı ölçmek için diğer alternatif yöntemler; gastrointestinal sistemden geçerken lümen içi basınç, pH ve sıcaklığı algılayan sindirilemeyen kablosuz motilite kapsül kullanımı ve 13C nefes testidir. Gastroparezi için klinik testler tanı için faydalı olsa da, sınırlı sayıdaki merkezlerde uygulanması, rutin klinik uygulama açısından zorlayıcı ve zaman alıcı olmalarının ötesinde, her zaman hastalardaki semptom ve bulgularla korele sonuçlar alınamadığı için tedavi sonuçlarının değerlendirilmesinde de sınırlı değerlere sahiptirler (4). Klinik pratik yaklaşımda; daha çok hastaların tariflediği semptom ve bulguları doğrultusunda takip ve tedavi uygulanmaktadır. Revicki ve ark. (4) tarafından gastroparezi tanılı 169 hasta GCSI anketi ile değerlendirildiğinde; semptomları şiddetli olan hastalarda GCSI anketi skorlarının daha yüksek olduğu saptanmıştır. Cassilly ve ark. (18) tarafından yapılan bir çalışmada, gastroparezi semptomları olan 226 hastanın GCSI anketi sonuçları incelendiğinde; bulantı-kusma semptom skorlarının, normal mide boşalması olan hastalara göre anlamlı derecede daha yüksek olduğu görülmüştür. Ancak anket sonuçlarında;

Tablo 3: Gruplar arası GCSI anketi sonuçları

	Grup 1, DM+, DPP-4-İ-, n=101	Grup 2, DM+, DPP-4-İ+, n=102	p-değeri
Bulantı/kusma skoru, ortanca (ÇA)	0 (0,7)	0 (0,7)	0,50
Erken doyma/postprandial tokluk hissi skoru, ortanca (ÇA)	0,5 (1,5)	0,3 (0,8)	0,048
Şişkinlik skoru, ortanca (ÇA)	0,5 (2)	0 (2)	0,24
Total skor, ortanca (ÇA)	0,6 (1,3)	0,3 (0,9)	0,14

+Ortanca (ÇA: Çeyrekler aralığı), Mann-Whitney U testi. P<0.05 için sonuçlar istatistiksel olarak anlamlı kabul edildi
DPP-4-İ: Dipeptidil peptidaz 4 enzim inhibitörleri, DM: Diabetes mellitus, GCSI: Gastroparezi Ana Semptom İndeksi, ÇA: Çeyrekler aralığı

Tablo 4: Diyabetik hastalarda spearman korelasyon analizi sonuçları

	Açlık kan glukozu		Tokluk kan glukozu		HbA1c		VKİ		Yaş		Diyabet hastalığı süresi	
	r_s	p-değeri	r_s	p-değeri	r_s	p-değeri	r_s	p-değeri	r_s	p-değeri	r_s	p-değeri
Bulantı/kusma skoru	-0,124	0,049	-0,250	<0,001	0,019	0,76	0,166	0,018	0,127	0,071	0,165	0,019
Erken doyma/ postprandial tokluk hissi skoru	-0,152	0,016	-0,096	0,17	-0,090	0,17	0,186	0,008	0,011	0,88	0,066	0,35
Şişkinlik skoru	-0,125	0,048	-0,072	0,30	-0,107	0,097	0,129	0,067	-0,076	0,28	0,050	0,48
Total skor	-0,153	0,015	-0,127	0,067	-0,076	0,24	0,202	0,004	0,005	0,94	0,110	0,12

$_s$: Spearman testi kullanılarak değişkenler arasında korelasyon analizi yapıldı. P<0.05 için sonuçlar istatistiksel olarak anlamlı kabul edildi
HbA1c: Hemoglobin A1c, VKİ: Vücut kitle indeksi

GCSI anketi toplam skor ortalaması için pozitif öngörü değeri sırasıyla %51 ile %61 arasında kalmıştır. Orijinal GCSI anketinin geliştirilerek 2 haftalık süre içerisinde günlük olarak sorgulandığı 5'i diyabetik hasta olan 12 katılımcıdan oluşan bir çalışmada hem diyabetik hem de diyabetik olmayan gastroparezi semptomları olan hastaların anket sorularını benzer şekilde anladıkları ve yorumladıkları bildirilmiş ve ankette semptom öğeleri setinin farklı gastroparezi etiyolojilerini kapsadığı kabul edilmiştir (19). Canpolat ve ark. (5) tarafından subklinik hipotiroidizmli hastalarda GCSI anketi ile yapılan sorgulamada kontrol grubuna göre total skor sonuçları daha yüksek saptanmıştır. Bizim çalışmamız ülkemizde GCSI anketi ile diyabetik hastalarda gastroparezinin değerlendirildiği ilk çalışmadır. GCSI anketinin orijinal çalışması ve anketin kullanıldığı diğer yayınlarla kıyaslandığında, çalışmamızda skorlar diyabetik olmayan hastalara göre daha düşük bulunmuştur.

T2DM hastalarında glisemik regülasyonu sağlayabilmek için kullanılan inkretin etkisini artıran ilaçların (DPP-4-İ,GLP-1RA) da gastroparezi gelişimi için ek bir risk faktörü olduğu düşünülmektedir (16). GCSI anketi ile değerlendirdiğimiz 203 diyabetik hastadan 102'si DPP-4-İ kullanırken,101'i DPP-4-İ almıyordu ve her iki grupta mikrovasküler ve makrovasküler komplikasyonlara yönelik yapılan incelemede anlamlı düzeyde farklılık saptanmadı. Kullanılan oral antidiyabetik tedavilere bakıldığında metformin kullanımı ve metformin + SGLT-2 kombinasyonu kullanımı dağılımının her iki grupta benzer olduğu görüldü. Ancak insülin tedavisi kullanımı DPP-4-İ$^+$'de %67,6 olarak daha yüksek tespit edildi (p=0,074). Ayrıca DPP-4-İ$^-$ gruptaki hastalardan GLP-1RA kullananlar çalışmaya dahil edilmedi. Her iki grupta HbA1c değerleri (p=0,101) ve VKİ'leri karşılaştırıldığında (p=0,35) anlamlı farklılık yoktu ve DPP-4-İ kullananlarda, GCSI anketi sonuçlarından erken doyma/ postprandial tokluk hissi bölümü ortalama skor anlamlı düzeyde daha düşük saptandı (p=0,048). Her iki grubun klinik bulguları ve uygulanan tedavi sonuçları değerlendirildiğinde; DPP-4-İ'nin, düşünülenin aksine erken doyma/postprandial tokluk hissi üzerine olumsuz etkileri olmadığı söylenebilir. Öte yandan GCSI anketi alt ölçeklerden, bulantı-kusma bölümü (p=0,50), şişkinlik bölümü (p=0,24), ve ortalama total skorun (p=0,14), DPP-4-İ$^+$ ve DPP-4-İ$^-$ hastalarda sonuçlarının benzer olduğu görüldü. Kullanılan DPP-4-i ilaçlar arasında da GCSI anketi sonuçları açısından anlamlı bir fark tespit edilmedi (p=0,50). DPP-4-İ'nin etkisi ile artan endojen inkretin hormonlarının gastrointestinal motilite üzerine etkileri hala tartışmalıdır. Aulinger ve ark. (20) tarafından 24 T2DM'li hasta ile yapılan randomize, plasebo kontrollü bir çalışmada oral sitagliptin kullanımının ardından yapılan oral glukoz tolerans testi sonrasında, DPP-4 inhibisyonunun etkileri ve glukoz düşürücü etkileri değerlendirilmiştir. DPP-4 inhibisyonuna bağlı insülin seviyelerinin ve inkretin etkisinin arttığı, glukagonun baskılandığı ve mide boşalmasının yavaşladığı görülmüştür. Ancak Stevens ve ark. (21) tarafından yapılan bir çalışmada ise sitagliptin kullanımı sonrasında, gastrik boşalma süresi etkilenmeden postprandial kan glukozunun azaldığı saptanmıştır. Diyabetik olmayan sağlıklı gönüllülerde 13C-asetik asit nefes testi kullanılarak sıvı mide boşalma hızının değerlendirildiği başka bir çalışmada; tek doz 50 mg sitagliptin oral alındıktan 2 saat sonra yenilen test yemeğinin ardından 150 dakika boyunca nefes örnekleri toplanarak mide boşalma hızı ölçüldüğünde, sitagliptin kullanımının sıvı mide boşalma hızı üzerinde anlamlı bir etkisinin olmadığı tespit edilmiştir (22). Ancak literatüre bakıldığında DPP-4-İ'yi kullanan diyabetik hastalarda GCSI anketi ile gastroparezi sorgulamasını değerlendiren çalışma bulunmamaktadır.

Çalışmada gastropareziyi değerlendiren ilave bir test (mide boşalma zamanı gibi) kullanılmamış olması ve literatürde yapılan çalışmalarda GCSI anketinin gastroparezi açısından pozitif öngörü değerinin sırasıyla %51 ile %61 arasında olması çalışmanın kısıtlılığını oluşturmuştur.

Sonuç

Çalışmamızda düşünülenin aksine diyabetik hastalarda DPP-4-İ'nin kullanımı sonrası gastroparezi semptom skorları daha düşük saptanmıştır. Ancak yaş, hastalık süresi, tokluk kan glukozu, HbA1c gibi değerler ile GCSI skorları arasında anlamlı bir korelasyon bulunmamasına rağmen, açlık kan glukozu düzeyi ile negatif yönde zayıf bir korelasyon ve VKİ ile ise pozitif yönde zayıf bir korelasyon saptanmıştır. Gastroparezi semptomlarını değerlendirmede invazif olmayan, poliklinikte rahatlıkla uygulanabilen ve maliyeti olmayan bir test yardımıyla gastroparezi değerlendirmesi yapılması amaçlanmış ancak, DPP-4-İ kullanımı ile gastroparezik semptomlar arasında ilişkili bulunamamıştır. Kullanılan DPP-4-İ ilaçlar arasında da GCSI anketi sonuçları açısından anlamlı bir fark bulunmamıştır. Bu çalışmada anket skorlarının anketin orijinal çalışması ve anketin kullanıldığı diğer yayınlarla kıyaslandığında düşük bulunmuş olması, sonuçları etkileyebileceği gibi, bu anketin diyabetik gastropareziyi değerlendirmede yetersiz kalabileceği ihtimalini de düşündürmüştür. Bu durum, DPP-4-İ'nin gastroparezi üzerine etkilerini ortaya koyabilmek için geniş ölçekli daha fazla çalışmalar yapılmasına ihtiyaç olduğunu göstermektedir.

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BASIC MEDICAL SCIENCES / TEMEL TIP BİLİMLERİ

TGF-β and Wnt Pathways Underlying the Pathophysiology of Degenerative Mitral Valve Regurgitation

Dejeneratif Mitral Yetmezliği Patofizyolojisinde Yer Alan TGF-β ve Wnt Sinyal Yolakları

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Abstract

Objectives: In aging society, hospitalizations and mitral valve surgeries are becoming more common due to progressive mitral valve diseases that ultimately lead to heart failure. In developing countries, degenerative mitral valve regurgitation (DMVR) is the leading cause of mitral regurgitation requiring surgical treatment. Nevertheless, a more profound understanding of the underlying pathological processes via a molecular biology approach could improve clinical management. In this study, bioinformatic analyses were performed to elucidate the underlying pathophysiological molecular mechanisms using transcriptome data of atrial tissues from patients with DMVR.

Materials and Methods: Bioinformatic analysis were done using GSE115574 dataset from The Gene Expression Omnibus (GEO) database. Transcriptome data which were downloaded from GEO database in CEL files generated from human left atrium and right atrium tissues in patients with DMVR in sinus rhythm (n=16) was used to perform bioinformatic analysis. Gene expression microarray analysis have done on Affymetrix platform previously. Bioinformatics, gene ontology, and functional enrichment analysis have been conducted on Partek GS V7.0 and WebGestalt software.

Results: The findings of this study reveal that multiple genes and various pathways play a role in the pathophysiology of DMVR. Among all transforming growth factor-beta (TGF-β) and Wnt signaling pathways enlightened according to false discovery rate thresholds and enriched geneset values. Prominent genes that involved in TGF-β and Wnt signaling pathways were *WNT5A*, *PLCB1*, *SFRP1*, *SMAD6*, *PITX2*, *SMAD7*, *ID2*, *BMP5*.

Conclusion: It's important to crystallize the molecular mechanisms of DMVR to facilitate early detection and develop targeted interventions. Management of TGF-β and Wnt signaling pathways in correct direction may offer solutions to slow DMVR progression and prevent it from becoming more complex.

Keywords: Mitral valve, TGF-β signaling pathway, Wnt signaling pathway

Öz

Amaç: Yaşlanan toplumlarda, en nihayetinde kalp yetmezliğine ilerleyen progresif mitral kapak hastalıkları nedeniyle hastaneye yatışlar ve mitral kapak ameliyatları daha yaygın hale gelmiştir. Gelişmekte olan ülkelerde, dejeneratif mitral kapak yetersizliği (DMVR) cerrahi tedavi gerektiren mitral yetersizliğinin önde gelen nedenidir. Bununla birlikte, altta yatan patolojik süreçlerin moleküler biyoloji yaklaşımıyla daha derinlemesine anlaşılması klinik yönetimi iyileştirebilir. Bu araştırmada, DMVR'li hastalardan alınan atriyum dokularının transkriptom verisi kullanılarak, altta yatan patofizyolojik moleküler mekanizmaları aydınlatmak amacıyla biyoinformatik analizler yapılmıştır.

Gereç ve Yöntem: Biyoinformatik analizler, Gen Ekspresyon Omnibus (GEO) veritabanından GSE115574 veriseti kullanılarak gerçekleştirilmiştir. Sinüs ritmindeki DMVR hastalarında (n=16) insan sol atriyum ve sağ atriyum elde edilen ve GEO veritabanından CEL dosyaları olarak indirilen transkriptom verisi biyoinformatik analizleri yapmak için kullanılmıştır. Gen ekspresyon mikroarray analizleri daha öncesinde Affymetrix platformunda gerçekleştirilmiştir. Biyoinformatik, gen ontolojisi ve fonksiyonel zenginleştirme analizleri Partek GS V7.0 ve WebGestalt yazılımlarında gerçekleştirilmiştir.

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Bulgular: Bu çalışmanın bulguları, DMVR patofizyolojisinde birden fazla genin ve çeşitli yolakların rol oynadığını ortaya koymaktadır. Tüm dönüştürücü büyüme faktörü-beta (TGF-β) ve Wnt sinyal yolakları arasında yanlış keşif oranı eşiklerine ve zenginleştirilmiş gen seti değerlerine göre aydınlatılmıştır. TGF-β ve Wnt sinyal yolaklarında yer alan öne çıkan genler *WNT5A*, *PLCB1*, *SFRP1*, *SMAD6*, *PITX2*, *SMAD7*, *ID2*, *BMP5* olarak tespit edilmiştir.

Sonuç: Erken teşhisi kolaylaştırmak ve hedefe yönelik müdahaleler geliştirmek için DMVR'nin moleküler mekanizmalarının tam olarak aydınlatılması önemlidir. TGF-β ve Wnt sinyal yolaklarının doğru şekilde yönetilmesi, DMVR progresyonunu yavaşlatmak ve daha karmaşık hale gelmesini önlemek için çözümler sunabilir.

Anahtar Kelimeler: Mitral kapak, TGF-β sinyal yolağı, Wnt sinyal yolağı

Introduction

Degenerative mitral valve regurgitation (DMVR) occurs leaflet malcoaptation during systole, leads to abnormal regurgitant flow from left ventricle to left atrium (LA). DMVR is a common valvular disorder characterized by the dysfunction of the mitral valve, resulting in the backward flow of blood from the left ventricle to the LA during systole. Hospitalizations and mitral valve surgeries have risen because of DMVR which is a progressive disease that eventually develops heart failure in the aging society (1). In developing countries, DMVR is the primary reason for mitral regurgitation that necessitates surgical intervention (2). Most common mechanisms underlying pathophysiology of DMVR are either fibroelastic deficiency of mitral valve or myxomatous degeneration of the mitral leaflets as in Barlow's disease (2). Remarkable consequences of DMVR are LA pressure and volume overload that leads to LA enlargement, a possible precursor of atrial fibrillation (AFib) due to the structural and electroanatomical remodeling. AFib is the most common arrhythmia and prevalence of AFib increases with aging (3). Also AFib has a negative progressive influence on DMVR prognosis (4). Chronic DMVR causes progressive LA enlargement, which negatively affects cellular coupling and electrical conduction and onsets AFib (5).

Current guidelines for intervention are mainly based on hemodynamic factors. However, a deeper insight into the underlying pathological processes through a molecular biology approach could enhance clinical management (6). In this study, we analysed transcriptomes of atrium tissues of DMVR patients using bioinformatic analyses. Differentially expressed genes were enriched in transforming growth factor-beta (TGF-β) and Wnt signaling pathways. The available knowledge identifies potential initial signaling pathways related to mechanical and biochemical triggers. These pathways determine the activation of specific transcription factors and subsequently modulate gene expression (7). DMVR is influenced by serotonin, TGF-β, and developmental pathways linked to heart valves, bones, and cartilage, such as bone morphogenetic protein (BMP) and Wnt signaling (8). Additionally, processes resembling osteogenesis and chondrogenesis may drive degenerative changes in aortic and mitral valves. Other implicated pathways include Notch, nitric oxide, and angiotensin II (9,10). The data of this study showed that gene expression profiles in atria of DMVR patients changed in different signaling pathways. Understanding the role of TGF-β and Wnt signaling pathways in the pathophysiology of degenerative mitral valve regurgitation is crucial for developing effective therapeutic strategies for this condition.

Materials and Methods

The raw microarray data, stored in CEL format files coming from transcriptomics of LA and RA tissues from 16 DMVR patients with sinus rhythm which were used as material that downloaded from Gene Expression Omnibus (GEO) database. Since CEL files downloaded from an open access functional genomics database were used as material in this study, there was no need for an ethics statement. The CEL files were uploaded to the Partek Genomic Suite® (PGS, V7.0, St. Louis, MO) (11).

Statistical Analysis and Bioinformatics

The preprocessing of the probe-level data was conducted and transformed using the Robust Multiarray Analysis algorithm. A fold change threshold of >1.5 and a p-value of <0.05 were set to identify differentially expressed transcripts. Adjusted p-values, known as q-values, were computed based on an optimized false discovery rate (FDR). A significance threshold for FDR was set at q<0.05. Furthermore, unsupervised hierarchical clustering was used to investigate the relationships between the LA and right atrial (RA) groups. Table listing the differentially expressed genes (DEGs) from LA versus RA comparison are available in Table 1.

Functional enrichment analysis were conducted using DEGs. Transcript IDs (Affy IDs) differentially regulated between LA and RA groups were uploaded to the WebGestalt (WEB-based Gene SeT AnaLysis Toolkit, http://www.webgestalt.org/) software. This platform was used for the annotation, enrichment, and visualization of these genes. gene ontology and pathway analyses were carried out using the WebGestalt toolkit. The functional enrichment analysis was executed using the overrepresentation analysis method and included adjustments for multiple tests with an FDR threshold of 0.05.

Results

The results of this study expose that several genes and different pathways are involved in the pathophysiology of DMVR. All patients participated to this study were in sinus rhythm during their operation (11). Atrium tissue transcriptomes were compared according to adjusted p-value <0.05 and fold change ±1.5 threshold. One hundred and ninety-eight Affy IDs were differentially expressed while 138 downregulated and 60 upregulated on Partek GS.

Functional enrichment analysis of DEGs from LA and RA tissues indicated that several KEGG pathways enlightened. Besides TGF-β and Wnt signaling pathways which are the focus of this study, retinol metabolism, glucagon signaling pathway, cell adhesion molecules, and chemokine signaling pathways are also enriched. But the geneset values or FDR thresholds were lower.

The genes from differentially expressed transcripts enriched in TGF-β and Wnt signaling pathways can be seen in Table 1. Affinity propagation of terms analysed by overrepresentation analysis are shown as volcano plot in Figure 1.

Table 1: The genes from differentially expressed transcripts enriched in TGF-β and Wnt signaling pathways

Affy ID	Gene symbol	Gene name	Entrez gene	Pathway geneset enriched
205990_s_at	*WNT5A*	Wnt family member 5A	7474	Wnt signaling pathway
213425_at	*WNT5A*	Wnt family member 5A	7474	Wnt signaling pathway
213222_at	*PLCB1*	Phospholipase C-β 1	23236	Wnt signaling pathway
202037_s_at	*SRFP1*	Secreted Frizzled related protein 1	6422	Wnt signaling pathway
219908_at	*DKK2*	Dickkopf Wnt signaling pathway inhibitor 2	27123	Wnt signaling pathway
210220_at	*FZD2*	Frizzled class receptor 2	2535	Wnt signaling pathway
207069_s_at	*SMAD6*	SMAD family member 6	4091	TGF-β signaling pathway
207558_s_at	*PITX2*	Paired like homeodomain 2	5308	TGF-β signaling pathway
204790_at	*SMAD7*	SMAD family member 7	4092	TGF-β signaling pathway
201565_s_at	*ID2*	Inhibitor of DNA binding 2	3398	TGF-β signaling pathway
205431_s_at	*BMP5*	Bone morphogenetic protein 5	653	TGF-β signaling pathway

TGF-β: Transforming growth factor beta

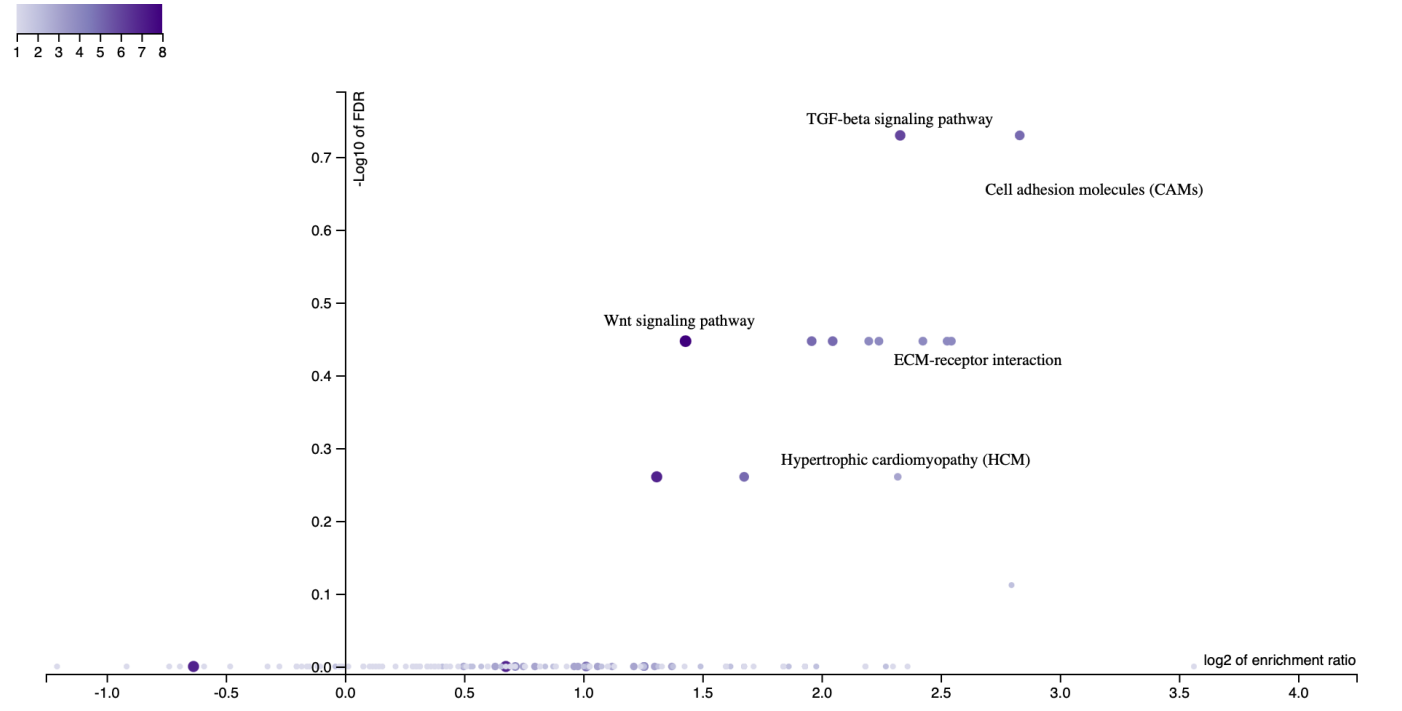

Figure 1: Affinity propagation of terms analysed by overrepresentation analysis are shown as volcano plot

ECM: Extracellular matrix, TGF: Transforming growth factor

Discussion

Reasons for progressing mitral regurgitation are divided into ischemic, which results from coronary artery disease, and nonischemic. The most frequent nonischemic causes of mitral regurgitation are degenerative in developed countries and, rheumatic in developing countries (12). During the early stages of valve degeneration, infiltrated inflammatory cells are frequently observed alongside elevated levels of proinflammatory cytokines like tumor necrosis factor-α, and interleukin-1β.

TGF-β Signaling Pathway

TGF-β is involved in various conditions including cardiac abnormalities, cardiac fibrosis, heart failure, chamber remodeling, and cardiac hypertrophy. The isoforms of TGF-β, along with activins, stimulate intracellular signaling through the SMAD2/3 transcription factors (13). Within the growth factor superfamily, the main subfamilies include TGF-β1, -β2, -β3 isoforms, BMPs, inhibins, and activins. Notably, the overexpression of TGF-β has been shown to play a significant role in various cardiac diseases characterized by fibrosis (14).

Differentially expressed geneset of this study's data functionally enriched in TGF-β signaling, which can be found on Kyoto Encyclopedia of Genes and Genomes pathway. TGF-β signaling is initiated by the dimerization of TGF-β, followed by its binding to TGF-β receptor type I (TGF-βR1) and type II (TGF-βR2). Specifically, numerous studies have identified elevated levels of TGF-β and increased expression of TGF-βR1 and TGF-βR2 in mitral regurgitation, observed in both human subjects and in vivo models (15,16). These findings have been thoroughly documented, establishing TGF-β as a key contributor to the myofibroblastic activation of valve interstitial cells when under tensile stress (17). This interaction forms a receptor heterocomplex that can recruit and phosphorylate SMAD proteins, thereby activating a variety of signal transduction pathways. SMAD6-7, molecules acting as inhibitors of SMAD1-5-8 play a significant role in preventing calcification (18). In this study, SMAD6 and SMAD7 are both downregulated which means TGF-β signaling inhibition is reduced in LA in DMVR patients. SMAD proteins are the major actor molecules in the TGF-β signaling pathway. Nuclear SMAD complexes work alongside DNA-binding transcription factors, as well as chromatin modifiers, to either positively or negatively influence the expression of genes responsive to TGF-β (19). The Wnt signaling pathway is a critical downstream pathway involved in TGF-β-mediated myocardial fibrosis. TGF-β triggers the secretion of Wnt and activates the Wnt/β-catenin signaling via the TGF-β activated kinase-1, which promotes the differentiation of myofibroblasts leading to myocardial fibrosis (20).

Wnt Signaling Pathway

There are two versions of Wnt signaling: canonical and non-canonical. Wnt signaling involves at least 19 Wnt ligands and 10 Frizzled receptors in humans, with the canonical pathway activated by Wnt ligands binding to Frizzled and either LRP5 or LRP6. This interaction stabilizes β-catenin, allowing it to accumulate and enter the nucleus to regulate gene expression through T cell-specific transcription factor/lymphoid enhancer-binding factor 1 (TCF/LEF) transcription factors. The Wnt signaling pathway consists of different components: the extracellular matrix, membrane, cytoplasmic part, and nuclear segments. Extracellular signals primarily involve *Wnt* genes like *Wnt3A*, *Wnt1*, and *Wnt5A*. The membrane component predominantly includes the Wnt receptors Frizzled (a specific seven-transmembrane receptor) and LRP5/6. The cytoplasmic component chiefly comprises β-catenin, the dishevelled genes (*DVL1*, *DVL2*, *DVL3*), glycogen synthase kinase-3β, and casein kinase I. The nuclear component mainly features β-catenin, which moves into the nucleus, members of the TCF/LEF family, and downstream target genes of β-catenin, such as MMPs and c-Myc. In canonical Wnt pathway dishvelled genes induces clustering of *LRP5/6*, Wnt, and Frizzled. Subsequently, balances β-catenin in the cytoplasm and *DVL* in the nucleus acts as a transcriptional regulator of *Wnt* target genes.

Wnt signaling plays a crucial role in embryogenesis and is activated when Wnt binds specifically to the Frizzled receptor and is stabilized by low-density lipoprotein receptor-related protein LRP5/6. This activation of the canonical Wnt pathway results in decreased degradation of β-catenin, which then moves to the nucleus to activate the TCF/LEF (21). Mutations in Wnt5A lead to mild heart defects by disrupting cell-cell adhesion and the organization of the cytoskeleton in cardiomyocytes as they differentiate (22). Wnt5A is a key player of non-canonical pathway and has been implicated to atherosclerotic progression (23).

Extracellular Wnt ligands can engage with various key antagonists that are secreted as well. Notably, these antagonists include the secreted Frizzled related proteins (SFRPs) and the Dickkopf proteins. The results of this study demonstrated that inhibitors of Wnt signaling were downregulated such as SFRP1 and DKK2.

Wnt signaling, which is essential for processes like bone and cartilage development, is regulated by at least five protein families that inhibit Wnt activity by targeting ligands, Frizzled, or LRP receptors (24). Specific ligands, such as Wnt3A and Wnt5A, are associated with chondrogenesis, while others promote osteogenesis (25). Studies showed that LRP5 mediates bone formation through inhibition of serotonin which directly

inhibits osteoblastogenesis (26). Dysregulated Wnt-LRP-5-β-catenin signaling has been implicated in calcific aortic valve disease, linking Wnt pathways to degenerative changes in valve tissues. Degenerative heart valve disease may mimic bone formation, resulting in osteogenesis in calcific aortic valves and chondrogenesis in myxomatous mitral valves (27). Recent findings suggest that serotonin, known to inhibit osteogenesis, might influence in this process by promoting chondrogenesis through serotonin expression in mitral valves which is leading to upregulation of TGF-β1, potentially preventing osteogenic changes (28). TGF-β1 upregulation enhances the production of extracellular matrix components like collagen and glycosaminoglycans.

Wnt signaling influences multiple pathways. In this study the expression of several modulators of the Wnt signaling pathway, such as Wnt5A, DKK2, and SFRP1, has been found differentially regulated in patients with DMVR.

The results of this study revealed increased regulation of TGF-β and Wnt signaling pathways in DMVR patient's atrial tissues. Understanding the triggers of degenerative valve disease and unraveling the complex interactions of signaling pathways may lead to the development of therapies targeted these pathways' triggers to slow or prevent disease progression.

Study Limitations

Bioinformatic enrichment tools are crucial for identifying, annotating, and analyzing large gene lists generated by high-throughput technologies like microarrays. While there may be minor variations between tools, the overall results are generally consistent, though subtle differences might occasionally be overlooked. Transcriptome profiling provides a precise snapshot of genome-wide mRNA expression at a precise moment and under the harvested time conditions but lacks predictive capability for downstream processes like translation, protein structures, interactions, and regulatory mechanisms. To address these limitations, complementary approaches such as protein interaction analysis are necessary to gain deeper insights. Additionally, global gene expression profiling using human or animal tissues faces challenges, particularly in accounting for metabolic processes influencing gene expression, a limitation inherent to tissue biopsy studies.

Conclusion

Degenerative calcific valve diseases are underestimated health issues. As the population ages and the absence of effective drug treatments, these conditions are expected to place an increasingly heavy strain on the global health system in the coming decades. Surgery option is just is to treat symptoms leaving the underlying pathophysiological mechanisms untouched. Further investigation should be done on clarifying molecular mechanisms underlying DMVR pathophysiology to detect disease in earlier stages and figure out intervention strategies on molecular triggers.

Ethics

Ethics Committee Approval: Since CEL files downloaded from an open access functional genomics database were used as material in this study, there was no need for an ethics statement.

Informed Consent: In this study, we analysed transcriptomes of atrium tissues of degenerative mitral valve regurgitation patients using bioinformatic analyses.

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Footnotes

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CASE REPORT / OLGU SUNUMU

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Anaplastic Multiple Myeloma: An Aggressive Myeloma Variant with A Poor Response to Autologous Stem Cell Transplantation

Anaplastik Multiple Miyeloma: Otolog Kök Hücre Nakli Tedavisine Yanıtsız Agresif Miyeloma Varyantı

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Abstract

Anaplastic multiple myeloma is an aggressive, chemotherapy-resistant subtype of myeloma with a poor prognosis. Approximately 2% of plasma cell myelomas are pleomorphic, anaplastic, and resemble metastatic tumor cells. Morphological differentiation of anaplastic cells is difficult, and immunohistochemistry and flow cytometry should be performed for immunophenotyping. We shared our experience with peripheral stem cell transplantation in this rare malignancy.

Keywords: Anaplastic multiple myeloma, CD38, Autologous stem cell transplantation

Öz

Anaplastik multipl miyeloma agresif seyirli, kemoterapilere dirençli, kötü prognozlu miyeloma alt tipidir. Plazma hücreli miyelomun yaklaşık %2'si pleomorfik, anaplastik özellikte olup metastatik tümör hücrelerine benzer. Anaplastik hücrelerin morfolojik ayırımı güç olup, immünfenotipleme için immünhistokimya ve akım sitometrik inceleme yapılmalıdır. Nadir görülen bu malignitede otolog periferik kök hücre nakil deneyimimizi paylaştık.

Anahtar Kelimeler: Anaplastik multipl miyeloma, CD38, Otolog kök hücre nakli

Introduction

Anaplastic multiple myeloma (AMM) is a type of multiple myeloma that is exceptionally scarce and aggressive. The prognosis of most AMM patients is poor, and the disease has a resistance to current chemotherapies (1). In this report, we present a case of an AMM patient with widespread metastasis and involvement of the extramedullary space who had poor outcomes with new myeloma therapies and autologous stem cell transplantation (ASCT).

Case Presentation

A man of 45 years of age was admitted to the hospital with swelling of the right breast, widespread pain, unintentional weight loss, night sweats, and fatigue for two months. The patient's past medical and family history was unremarkable. Physical examination showed localized tenderness of palpable mass. The positron emission tomography-computed tomography scan demonstrated a 15x12 cm mass involving the right anterior chest wall, destructing the 4th and 5th costas with an standardized uptake value 20.7, and abnormal ^{18}Fluorine-fluorodeoxyglucose intake of the right axillary, internal mammary, parasternal,

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retrosternal, pericardiac, supradiaphragmatic lymph nodes, 5th and 8th costas. A trucut biopsy pathology revealed that large atypical cells with pleomorphic nuclei, a moderate amount of polarized cytoplasm, and common necrotic areas infiltrated the fibrous and muscular tissues. Immunohistochemical staining showed the tumor tissue was positively stained for CD138, multiple myeloma oncogene 1 (MUM-1), CD45 (LCA), CD117, vimentin, lambda light chain, and negatively stained for CD3, CD4, CD15, CD20, CD30, CD38 CD56, PAX5, TDT, desmin, actin. The in situ hybridization for the Epstein-Barr virus-encoded RNA was negative. The Ki-67 proliferation index was exceedingly high (100%) (Figure 1). Cytogenetic analysis demonstrated no abnormality for multiple myeloma. Bone marrow was not involved. From these findings, the patient was reported to have AMM.

The laboratory examination showed an average blood count with a hemoglobin of 14.8 g/dL. Biochemical tests demonstrated that albumin, 3.6 g/dL (normal range 3.5-5.2); total serum protein, 6.5 g/dL (normal range 6.6-8.3); mildly elevated beta-2 microglobulin, 2.82 mg/L (normal range 1.16-2.52), and lactic dehydrogenase, 272 U/L (normal range 0-248); serum renal and liver function tests were in the normal range. The results of the serological tests for Epstein-Barr virus, human immunodeficiency virus, hepatitis B, and hepatitis C were all negative. Serum and urine protein electrophoresis and immunofixation analysis revealed no monoclonal bands. There was an increase in the free lambda light chain level in the serum [39.1 mg/L (normal range 5.71-26.3)], but no change in the kappa/lambda ratio [0.24 (normal range 0.26-1.65)].

The patient received a VCD regimen of a 21-day cycle, including bortezomib 1,3 mg/m^2 per week, cyclophosphamide 300 mg/m^2 per week, and dexamethasone 40 mg/day (d) (on d1, d4, d8, d11). After three cycles of VCD, the disease progressed rapidly with right pleural effusion. Our patient underwent 3500 cGy of radiation therapy with the RD regimen (lenalidomide 5 mg/day for 21 days, dexamethasone 40 mg/week). After two cycles of the RD regimen, the patient achieved partial remission, and severe dyspnea improved. Because of the CD38 negativity, we did not offer daratumumab-based regimens. High-dose chemotherapy (cyclophosphamide, 60 mg/kg on d-5, d-6; total body irradiation, 2x2 Gy/day on d-3, d-2, d-1) with ASCT was sequentially performed and achieved very good partial remission (VGPR). Two months later, the disease progressed quite aggressively, and the patient died of infectious causes after surviving 11 months from the time of diagnosis.

Discussion

AMM usually presents in young patients and is commonly characterized by an extramedullary involvement and immunoglobulin A isotype (2). AMM cells are usually positively stained for CD38, CD138, MUM1 and negatively stained for CD3, CD19, and CD20, which is consistent with our patient, except CD38 negativity. AMM and the CD38 negativity have been documented at diagnosis in several cases (4-6). This very rare CD38 negativity delays diagnosis and blocks the anti-CD38 therapy, so CD38 negative AMM are even more aggressive than CD38+ ones, and the absence of CD38 expression is linked to relapsed/refractory conditions (4-6). A patient with CD38 negative and (4;14) translocation died before initiating treatment (5).

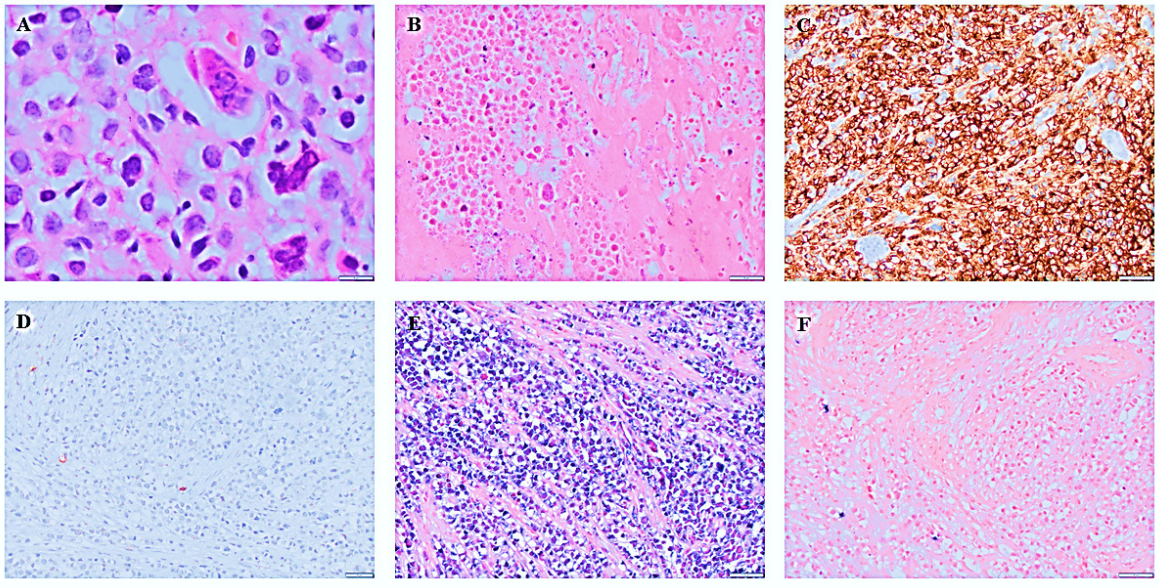

Figure 1: Pathological findings. **(A)** Tumour hematoxylin and eosin staining showed large atypical anaplastic cells (1000×). **(B)** Diffuse and severe coagulative necrosis in neoplastic infiltration (400×). Immunohistochemistry showed that the tumor cells were **(C)** CD138+, **(D)** CD 38-, **(E)** Lambda light chain+, and **(F)** Kappa light chain- (200×).

AMM demonstrates resistance to conventional chemotherapy, radiotherapy, and novel myeloma therapies (e.g., daratumumab, carfilzomib); in contrast, some reported cases had a relatively long-term outcome (1,3,7-10). In the study by Huang et al. (3), a patient treated with a combination of bortezomib and conventional chemotherapy survived for nine months. Another AMM patient with hepatic dysfunction was monitored for thirty months with RD maintenance therapy after VCD treatment, achieving a VGPR (9). A 70-year-old patient achieved a complete response after four cycles of VRD and was followed in remission for four months (10). Conversely, in the case report by Saburi et al. (8), a patient with AMM, 17p deletion, and CD38 positivity did not respond to treatments based on daratumumab and carfilzomib.

ASCT has been planned in which patients had a response to previous therapy, but they could not proceed because of rapid clinical deterioration (7,11). Ichikawa et al. (1) reported a case who received the four cycles of *etoposide, doxorubicin, vincristine, prednisolone, and cyclophosphamide*-EPOCH regimen with a VGPR response followed by ASCT resulted in six months remission. Our case received radiotherapy, bortezomib, and lenalidomide-based therapies followed by ASCT, which resulted in a VGPR response. However, the disease relapsed within two months after transplantation.

The remission status of the patient with AMM is the key to success. Using novel agents, cellular immunotherapies, and bispecific antibodies to reach this goal is a mission in progress, and the disease pathophysiology and genomic pathways need to be understood.

Ethics

Informed Consent: The Ankara University Human Research Ethics Committee approved this article (date: 10.12.2021, approval no.: İ11-690-21).

Authorship Contributions

Surgical and Medical Practices: D.K., İ.Ö.D., I.K., S.K.T., T.D., Concept: D.K., M.O., Design: D.K., Data Collection: D.K., Literature Search: D.K., M.O., Writing: D.K.

Conflict of Interest: The authors declare that there were no conflicts of interest during the preparation and publication of this article.

Financial Disclosure: The authors declared that they did not receive any financial support during the research and authoring of this article.

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Ali Ersin Zümrütbaş
Ali Murat Tatlı
Alp Can
Alper Bayazıt
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Asutay Orak Göktuğ
Ata Ecevit
Ata Niyazi Ecevit
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Oya Tekeli
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Ömer Gülpınar
Ömer Kurtipek
Özgür Kartal
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Pınar Karabak Bilal
Ramazan Erdem Er
Rıfat Vedat Yıldırım
Safa Dönmez
Safiye Gürel
Sena Ünal
Serap Şahinoğlu
Serap Teber
Serdar Alan
Serhat Erol
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