Medicine and Health Sciences Researches

Editors

Nizami DURAN

Canan DEMİR

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Editors • Prof. Dr. Nizami DURAN • Orcid: 0000-0002-2766-3491
Assoc.Prof. Dr. Canan DEMİR • Orcid: 0000-0002-4204-9756
Cover Design • Motion Graphics
Book Layout • Mirajul Kayal

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website • http://www.livredelyon.com
e-mail • livredelyon@gmail.com

PREFACE

This book is a significant reference work that covers a wide range of areas within health sciences. It comprises 19 chapters that offer comprehensive and current information on basic and clinical medical sciences, pharmaceutical sciences, dental clinical sciences, physical medical sciences, and health sciences. It is a valuable resource for undergraduate and graduate students and academics studying in these fields.

Each chapter includes beneficial information and references that can assist young researchers in developing and expanding new ideas. The book is an easy-to-use guidebook that has compiled current information in various fields of health sciences. We want to thank the chapter authors for their contributions in making this book an extraordinary resource.

Editors

Prof.Dr.Nizami DURAN
Hatay Mustafa Kemal University, Medical Faculty,
Department of Medical Microbiology
Antakya-Hatay

Assoc. Prof. Dr. Canan DEMİR
Van Yüzüncü Yıl University
Van Health Services Vocational School
Van

CONTENTS

CHAPTER I

TARGETED THERAPİES İN NON-SMALL CELL LUNG CANCER

Şebnem YILDIRIMCAN KADIÇEŞME

(Asst. Prof. Dr.), Kafkas University, Faculty of Medicine, Department of Medical Biology, Kars, Turkey.
E-mail:sebnem.yildirimcan@kafkas@edu.tr
ORCID: 0000-0002-8908-9464

1. Introduction

Nowadays, one of the biggest health problems is cancer. Although lung cancer was uncommon in the early 1900s, it is now a significant health concern. In terms of cancer-related mortality in men, lung cancer ranks first, and in women, it ranks second. (1, 2)

Non-small-cell lung cancers (NSCLCs) account for about 85% of instances of lung cancer. The use of biomarkers in the diagnosis and treatment of NSCLC has expanded recently due to the growing advancements in molecular biology. About 25% of NSCLCs have oncogenic alterations, which can be addressed with targeted therapy. (3)

Targeted therapies aim to overcome many challenges encountered with conventional treatments in addressing NSCLC. (3)

2. Non-Small Cell Lung Cancer

Lung cancer emerges through a multistep carcinogenesis process involving genetic and epigenetic alterations. Lung cancer is the primary cause of these deaths, responsible for 18% of cancer-related deaths worldwide. (1)

Chest pain, sputum, exhaustion, appetite loss, dyspnea, and shortness of breath are among the most common signs and symptoms of lung cancer. Its etiology involves significant roles of factors such as smoking, environmental exposures, radon, air pollution, occupational factors (asbestos, arsenic, aluminum, nickel, chromium, radiation), viruses, lung diseases, and genetic

susceptibility. (4) Lung cancer is less common in young people and increases with age. It has a poor prognosis, with only 10-15% of cases surviving for five years or longer. When the diagnosis was made, over 40% of cases of lung cancer had distant organ metastases; the brain, adrenal glands, liver, bones, kidneys, thorax, and abdominal lymph nodes were the most frequently seen metastatic locations. (5,6)

While there are many histological subtypes of lung cancer, clinical evaluation usually concentrates on NSCLC and small cell lung cancer (SCLC) in order to establish the therapeutic strategy. About 85% of instances of lung cancer are classified as NSCLC, with squamous cell carcinoma, adenocarcinoma, and large cell carcinoma being the most prevalent subtypes. Due to significant variations in treatment and prognosis, it is necessary to be able to distinguish between NSCLC and SCLC when developing efficient treatment methods. (7)

After a lung cancer diagnosis, staging the disease is essential for providing a sound prognosis, determining the most effective treatment approach, and scientifically comparing treatment outcomes. The TNM system is used for staging NSCLCs. In this system, T represents the primary tumor, N denotes regional lymph nodes, and M indicates distant metastasis. The initial tumor's size and degree of local invasion are classified by the T component, regional lymph node involvement is indicated by the N component, and metastasis is indicated by the M component. (6) Cases are grouped into stages 0, I, II, III, and IV based on their T, N, and M statuses. In Stage I, cancer is only in the lungs with no lymph node involvement. Cancer has spread to neighboring lymph nodes in Stage II. In stage 3, there is spread to the space between both lungs and the lung membrane (pleura), and in stage 4, there is spread to organs such as bone, liver and adrenal glands. (8,9)

Determining the cell type and accurately staging the disease are crucial for applying the most appropriate treatment in cases. Factors such as age, performance status, gender, weight loss, cell type, genetic factors, and tumor stage influence the prognosis of lung cancers. As we progress from stage I to IV, the prognosis worsens. In Stage I, II, and IIIA (T1-3 N1 M0) NSCLC cases, surgery is the most effective treatment method for ensuring survival. If necessary, chemotherapy and radiotherapy may be applied before and after surgery. (10)

3. Targeted Therapies in Cancer

The onset, progression, prognosis, and susceptibility to cancer are significantly influenced by genetic factors. Understanding the genetic

mechanisms involved in the disease is highly important for both diagnosis and treatment approaches. (11)

Today, the most commonly used treatment methods for various clinically diagnosed cancer types (leukemia, skin, head-neck, brain, lung, kidney, prostate, breast, ovarian, stomach-intestinal system, etc.) include surgical removal of tumor tissue, radiotherapy, and chemotherapy. While classical treatment approaches are effective in the initial stages, resistance to treatment is encountered when cancer metastasizes, leading to patient loss due to relapse. Chemotherapy poses serious toxicity issues, killing all dividing cells and causing severe side effects. Additionally, chemotherapy resistance reduces survival time. In recent years, targeted treatment approaches have been emphasized to overcome these problems in the treatment process. Targeted therapies aim to reduce toxicity, increase drug effectiveness through specific treatment for cancer cells, and extend survival time. (12)

In order to stop cancer from growing, developing, and spreading, targeted therapy involves administering medications that specifically target chemicals involved in the emergence, growth, development, and spread of cancer cells. (11)

4. Molecular Targets in Non-Small Cell Lung Cancer

Among the main molecular alterations observed in NSCLC are the inactivation of tumor suppressor genes, the activation of oncogenes, alterations to genes involved in DNA repair and cell cycle regulation, as well as changes affecting growth factors and receptors. Targeting these molecular changes aims to achieve personalized treatment for individuals with NSCLC. (13)

Targeted therapy is affected by genetic alterations found in NSCLC, including mutations in the *EGFR, ALK, KRAS, HER2, RET, ROS1*, and *BRAF* genes. After identifying patients carrying these mutations, targeted therapies can be applied to these individuals. (14)

4.1. EGFR Mutation

The transmembrane glycoprotein with tyrosine kinase activity known as the epidermal growth factor receptor (EGFR) is encoded by the *EGFR* gene, which is found on 7p12 and has 28 exons. One essential signaling molecule that controls both cell division and death is EGFR. (15)

After ligands (EGF and TGFα) bind to EGFR, the tyrosine kinase domain inside the cell becomes activated. Afterwards, signals for cell growth and

division control and anti-apoptotic signals are sent to the nucleus via downstream signaling pathways (mTOR/PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, and JAK/STAT). (16)

Mutations in the *EGFR* tyrosine kinase domain result in increased receptor tyrosine kinase activity. As a consequence, activation of the PI3K/AKT, JAK-STAT, and ERK/MAPK pathways occurs, triggering carcinogenesis. (17)

Point mutations in exon 21 (L858R) and deletions in exon 19 (del 746–A750) account for about 85–90% of all *EGFR* mutations. (17) Women, nonsmokers, and people of East Asian descent are more likely to carry these mutations in NSCLC, especially those of the adenocarcinoma subtype. (18)

Tyrosine kinase inhibitors (TKIs) are often used during EGFR-targeted therapies. Tyrosine kinase activity is inhibited by these inhibitors, and downstream signaling pathways are blocked as a result. Consequently, they stimulate apoptosis and prevent tumor cells from proliferating and metastasizing.

Currently, three generations of TKIs are available for therapeutic use. The first generation of reversible inhibitors includes icotinib, gefitinib, and erlotinib. Dacomitinib and afatinib are second-generation inhibitors, while osimertinib, almonertinib, and lazertinib belong to the third generation of irreversible inhibitors. (16)

Tyrosine kinase domain mutation patients usually respond to *EGFR* TKIs at a rate of about 70%. (15) TKIs have been shown to be a more effective first-line treatment than chemotherapy for individuals with *EGFR* mutations. As a result, patients with *EGFR* mutations typically start *EGFR* TKIs as their first line of treatment. (19)

Resistance can develop in patients receiving *EGFR* TKI treatment, particularly due to secondary mutations (such as T790M) and amplification of the *MET* oncogene. Irreversible TKIs (lapatinib, neratinib, and afatinib) and MET inhibitors are two methods for overcoming *EGFR* TKI resistance. Patients who become resistant to *EGFR* TKIs may experience a decline in therapy response rates and a fall in overall survival. (14)

The combination of targeted EGFR therapy with antiangiogenic therapy is an effective strategy in the treatment of NSCLC. Solid tumor growth and dissemination depend on the process of angiogenesis. Numerous cancer types have shown better survival when vascular endothelial growth factor (VEGF), a crucial component of tumor angiogenesis, is targeted. For advanced NSCLC, dual inhibition of EGFR and VEGF is a successful therapy approach. (16)

4.2. ALK Fusion Mutations

The *ALK* gene (2p23) encodes anaplastic lymphoma kinase (ALK), a member of the receptor tyrosine kinase insulin receptor superfamily. The ALK protein plays significant roles in brain development and the nervous system. Rearrangements of the *ALK* gene are frequently observed in NSCLC. As a result of these rearrangements, fusion genes are formed, most commonly involving *EML4* (Echinoderm microtubule-associated protein-like4), responsible for microtubule binding. The first fusion gene discovered in NSCLC in 2007 was the *EML4-ALK* Fusion Gene, which results from an inversion on 2p. (16)

To date, a total of 27 *ALK* fusion variants have been identified, with 21 of them belonging to *EML4*. *ALK* can also form fusions with genes such as *KLC1, TFG*, and *KIF5B*. As a result of fusion gene formation, constitutive activation of *ALK* tyrosine kinase occurs. As a result, aberrant activation of oncogenic signaling pathways (including EGFR, KIT, JAK/STAT3, MEK/ERK, and PI3K/AKT) is seen, which promotes invasion, enhances cell proliferation, and inhibits apoptosis. (16)

ALK positivity, or rearrangements involving *EML4-ALK*, is found in about 4% of NSCLC. They are more prevalent in women, Asian populations, non-smokers, and the adenocarcinoma subtype. (15)

Using *ALK* inhibitors is the main therapy strategy for patients who test positive for *ALK*. The first *ALK/MET* TKI to be used in clinical practice is crizotinib. It triggers apoptosis and leads to tumor shrinkage. (20) Studies suggest that it is more effective than chemotherapy and contributes to a more successful outcome in terms of survival in *ALK*-positive patients. (16)

A powerful second-generation TKI is called cetinib. When used as the first-line treatment for advanced NSCLC that is positive for *ALK*, ceritinib, as approved by the FDA in 2017, was found to improve survival rates. (21) Alectinib and Brigatinib are also second-generation *ALK*-targeted TKIs. Lorlatinib is a third-generation inhibitor. (21)

Just like in *EGFR*, resistance can develop against *ALK* TKIs as well. (22) Efforts are ongoing to develop new treatments to overcome resistance mechanisms. (16)

4.3. HER2 Mutations

Situated on 17q12, the *HER-2* gene encodes a transmembrane tyrosine kinase receptor. HER2 is a member of the ERBB family and is

involved in signaling pathways that regulate cell survival, proliferation, and differentiation. (23)

HER2 mutations are present in 1-3 percent of NSCLC. In cases negative for *EGFR, ALK*, and *KRAS*, around 6% exhibit *HER2* mutations. *As a result of HER2 mutations, defects in ligand binding lead to the formation of dimers with other receptors of the ERBB family, and autophosphorylation occurs.* Autophosphorylation activates downstream signaling pathways (PI3K, MAPK, and JAK/STAT), resulting in uncontrolled cell proliferation and tumor formation. (23)

HER2 is activated by protein overexpression, gene amplification, and gene mutation. An in-frame insertion in exon 20 (A775_G776insYVMA) is the most common *HER2* mutation detected in NSCLC. *HER2* mutations are more common in women, those of Asian heritage, non-smokers, and those with adenocarcinomas. (15,16)

There are several approaches targeting *HER-2* molecular alterations. Afatinib and dacomitinib are TKIs used in *HER2*-targeted therapy. Humanized monoclonal anti-HER2 antibodies (trastuzumab and pertuzumab) bind to the HER extracellular domain and inhibit dimerization. They lead to decreased cell proliferation and increased apoptosis. Trastuzumab and pertuzumab have demonstrated insufficient efficacy in treating NSCLC, despite their effectiveness in treating cases of HER2-positive breast cancer. (16)

In recent years, the effects of new *HER2* TKIs have been under investigation. For example, poziotinib (a novel selective *HER 2* TKI) has been shown to be effective in patients with *HER 2* exon 20 mutations. Additionally, NSCLC patients with *HER 2* mutations have demonstrated good therapeutic outcomes with antibody-drug conjugates (ADCs). (16)

One sort of antibody-drug conjugate (ADC) that binds to trastuzumab, a cytotoxic microtubule inhibitor, is called trastuzumab-emtansine (T-DM1). Combining monoclonal antibody medications with cytotoxic medications can help reduce toxic and adverse effects while improving therapy efficacy. (16)

Another ADC drug is trastuzumab-deruxtecan (T-DXd, DS-8201). *HER 2* mutation-positive NSCLC patients have shown a good response to this medication, which consists of an anti-HER2 antibody plus a topoisomerase I inhibitor. T-DXd has received FDA approval for targeted treatments in *HER2* mutant NSCLCs.

Research is being conducted to create a variety of new drugs targeting *HER2* to prolong the lives of NSCLC patients with *HER2* mutations. (16)

4.4. BRAF Mutations

The BRAF protein, which is produced by the *BRAF* gene (B-Raf proto-oncogene) and participates in the RAS/MAPK signaling pathway, is responsible for sending chemical signals from the exterior of the cell to the nucleus. The RAS/MAPK signaling system is involved in the control of apoptosis, migration, differentiation, and proliferation of cells. Mutations in the oncogene *BRAF* may contribute to the onset and spread of cancer. (24)

BRAF V600 mutations have been found to be present in 3–5% of instances of NSCLC. The exon 15 V600E mutation is present in around 50% of *BRAF* V600 mutations. This mutation causes the MAPK pathway to be constitutively activated, which in turn causes cancer. The V600E mutation is more frequently observed in non-smokers and female patients. There are non-V600 *BRAF* gene mutations (K601, L597, G464, etc.) in almost half of individuals with NSCLC. (22,24)

For NSCLC patients with *BRAF* mutations, standard chemotherapy is not very successful. Targeted therapy is more effective in these patients. Although *BRAF* TKIs (Dabrafenib and Vemurafenib) have been used for the treatment of patients carrying *BRAF* mutations, various resistance problems are encountered during the use of these drugs in patients. Efforts are ongoing to overcome these problems and develop more effective treatments. (24)

4.5. ROS1 Fusion Mutations

The ROS1 gene encodes the transmembrane tyrosine kinase receptor (ROS 1), which is involved in cell proliferation and differentiation. Signals via the PI3K/AKT/mTOR, STAT3, and RAS/MAPK/ERK pathways are transmitted by the ROS1 receptor. (15)

ROS1 rearrangement is observed in approximately 0.9–2.6% of NSCLC cases. EZR (13–24%), *SDC4* (9–13%), *CD74* (38–54%), and *SLC34A2* (5–10%) are often found fusion partners in *ROS1*-positive NSCLC.

Especially in adenocarcinomas, women, non-smokers, and young patients, ROS1 fusions are more frequently encountered. (3)

Since 2016, crizotinib (TKI) has been the reference in first-line treatment, with more than half of the patients responding to the treatment. Crizotinib, despite being highly successful in the treatment of NSCLC, poses some challenges due to its weak brain penetration. For example, brain metastases are present in about 36% of patients who test positive for ROS1 at the time of

diagnosis. Consequently, targeted compounds like entrectinib, lorlatinib, etc. that have improved brain penetration have been produced. (3)

Entrectinib, a multikinase inhibitor that can penetrate the blood-brain barrier, targets *ROS-1, ALK*, or tropomyosin-receptor kinase. The European Medicines Agency (EMA) and the FDA both approved it in 2019. In 2020, its temporary use was permitted for treating adults and children over 12 years old. (3) Ceritinib, Cabozantinib, Repotrectinib, and Brigatinib are also other TKIs. (21)

4.6. RET fusion Mutations

The receptor tyrosine kinase encoded by the *RET* proto-oncogene is necessary for the proper growth of several types of nerve cells, including enteric neurons.

RET fusion mutations are seen in 1% to 2% of NSCLC. 72% of instances are caused by the *KIF5B-RET* fusion gene, which results from the 10p11.22-q11.21 pericentric inversion. (14,15) It is commonly observed in young, non-smoking individuals with adenocarcinoma cases.

The FDA or EMA has approved some selective TKIs in order to cure patients with NSCLC who have *RET*-fusion positivity. (25,26)

4.7. KRAS Mutations

The *RAS* protooncogene family member KRAS (K-Ras), which is associated with the RAS/MAPK pathway, encodes the K-Ras protein. This protein is responsible for the conversion of GTP to GDP, playing a role in cell growth, proliferation, and differentiation by transmitting signals from outside the cell to the nucleus. (21)

The most prevalent oncogenic changes, found in 25–40% of adenocarcinomas, are KRAS mutations. Missense mutations in *KRAS* codons 12, 13, and 61 are frequently observed in NSCLC. Through constitutive activation of the RAS signal, these mutations alter the PI3K/Akt and MAPK signaling pathways, resulting in aberrant tumor growth. (14,16)

The frequent occurrence of *KRAS* mutations has made it a therapeutic target in lung cancer. Despite numerous failures in studies targeting *KRAS*, recent years have seen the development of new agents focusing on this mutation. To treat patients with *KRAS* G12C mutations (39–41%), which are widespread in NSCLC, the FDA authorized Sotorasib (LUMAKRAS) in 2021. (27,28)

5. Conclusion

Targeted therapies are an effective treatment strategy for NSCLC. However, there are still many problems to be solved, such as resistance mechanisms and various side effects encountered in these treatments.

As molecular biology advancements progress in the understanding of NSCLC, an increase in molecular markers used for diagnosis and treatment is anticipated. This will, therefore, result in the creation of more focused and successful treatment plans.

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CHAPTER II

LONG NON-CODING RNAS

Ali Erdinç YALIN[1] & Serap YALIN [2]

[1](Prof. Dr.), Mersin University,
E-mail: aeyalin@gmail.com,
ORCID: 0000-0002-3351-6885

[2](Prof. Dr.), Mersin University,
E-mail: syalin@mersin.edu.tr,
ORCID: 0000-0002-1286-2172

1. Introduction

RNA is a nucleic acid that plays several crucial roles in cellular functions, such as the transmission of genetic information and protein synthesis within cells. It contributes significantly to the process of genetic information transfer. The tools and mechanisms involved in RNA synthesis vary between eukaryotes and prokaryotes. Specific RNA molecules also regulate gene expression and have the potential to serve as therapeutic agents in the treatment of human diseases (1). The genetic information in the cell's DNA is transferred to RNA through a process called transcription, where RNA serves as a copy of the DNA. This RNA is then transported to the cytoplasm of the cell to be used in the process of protein synthesis. A process called translation, which occurs in cellular organelles called ribosomes, converts RNA into the protein structure (2). mRNA, rRNA, and tRNA are the three main types of RNA involved in protein synthesis. RNA also plays a primary role as the genetic material for viruses. Other functions of RNA include RNA editing, gene regulation, and RNA interference, which are carried out by a group of small regulatory RNAs including small nuclear RNA, microRNA, and small interfering RNA (3).

2. Non-Coding RNAs

Non-coding RNAs are transcribed from genomic DNA and do not participate in protein production. Non-coding RNAs serve as critical regulators in cell death and development. RNA consists of both messenger RNA (mRNA), which is translated into proteins, and non-translated non-coding RNA regions. The majority of RNA, more than 98%, cannot be translated into proteins, with more than 70% of these non-translatable regions being introns (4).

In recent years, non-coding RNAs have become a significant area of research. Currently, the number of non-coding RNAs identified only in mammals exceeds 20,000. These non-coding RNAs play various regulatory, and functional roles within the cell. They contribute significantly to many biological processes such as the cell cycle, development, and disease progression (4-6).

2.1. Classification of Non-Coding RNAs Based on Size

Non-coding RNAs longer than 200 nucleotides are referred to as "long non-coding RNA" (lncRNA), while those shorter than 200 nucleotides are called "small non-coding RNA" (7). Despite lacking the ability to code for proteins, lncRNAs share many similar features with coding transcripts. Therefore, lncRNAs can contribute to a wide range of biological processes, including apoptosis, cell cycle regulation, genomic imprinting, splicing, epigenetic regulation, cell development, and differentiation (6).

Recent research suggests that lncRNAs may have oncogenic or tumor-suppressive functions in cancer development and progression. This underscores their significant role in various processes associated with cancer. As potential therapeutic targets in cancer treatment, they can be evaluated for their use as biological markers to predict relapse and prognosis (8).

2.2. The Most Common Types of Non-Coding RNAs Based on Their Functions

Long Non-Coding RNA (lncRNA):

These molecules can play roles in various biological processes, including the regulation of gene expression, chromatin structure, transcriptional regulation, and mRNA processing (9,10).

Small Interfering RNA (siRNA):

siRNAs participate in a process called RNA interference (RNAi). Synthesized within the cell or administered externally, siRNA molecules match specific mRNA targets, leading to their degradation and thereby suppressing gene expression (11).

siRNAs are formed from long double-stranded RNAs with the assistance of Dicer (Dicer: a crucial enzyme in RNAi and microRNA biology) (4,12). Often synthetically generated in laboratories, siRNAs are administered to cells externally with the aim of silencing specific genes. Active in the RNAi process, siRNAs, short double-stranded RNA fragments, specifically bind to the mRNA of the target gene, leading to its destruction or inhibition of its function within the cell. Due to their potential ability to eliminate genes, siRNAs have the potential to be therapeutic agents for diseases (13,14).

Piwi-Interacting RNA (piRNA):

Found in germ cells, these RNAs have a crucial function in controlling transposons (mobile genetic elements). They become active to maintain genome stability and suppress the movement of transposons (15).

Small Nucleolar RNA (snoRNA):

snoRNAs are mainly encoded by intronic regions of both protein coding and non-protein coding genes. They have non-coding functions such as catalyzing chemical modifications of ribosomal RNA and participating in ribosome formation (11, 13).

MicroRNA (miRNA):

miRNAs are non-coding RNA types. They have non-coding functions, such as regulating gene expression, influencing protein synthesis, and playing significant roles in the cell cycle, development, and disease processes (13).

miRNAS are approximately 18-22 nucleotides in length, regulating gene expression at the post-transcriptional level. These molecules bind to their target mRNAs based on complementarity principles. A single miRNA can target multiple mRNAs. If the complementarity between miRNA and the target mRNA is perfect or nearly perfect, the miRNA cleaves the target mRNA, whereas partial complementarity suppresses the translation of the target gene.

They are mostly processed from introns and copied from the host gene into primary miRNA by RNA polymerase II (16). Subsequently, endonucleases

like Drosha and Dicer transform them into mature miRNAs. Studies have shown that miRNAs binding to the untranslated region (3'UTR) of mRNAs can suppress translation, while miRNA binding to promoter regions can upregulate transcription (16). miRNAs can also function similarly to hormones, being released into extracellular fluids and taken up by target cells to regulate cellular activity. Additionally, researchers consider extracellular miRNAs as potential biomarkers for various diseases (17). Studies have indicated the involvement of circulating miRNAs in controlling oncogenes and tumor suppressors, thereby playing a role in cancer (13,18,19).

miRNAs can be classified as intergenic or intronic. Intergenic miRNAs have independent transcription units with their own promoters. In contrast, intronic miRNAs share the same promoter with their host genes (19).

Next-generation sequencing technologies have significantly impacted non-coding RNA research. While microarray applications are also used in non-coding RNA studies, microarray technology is limited to the identification of known miRNAs and siRNAs. Due to the abundance of various types of non-coding RNAs, statistical limitations arise in the statistical identification of new non-coding RNA genes. Short sequence sequencing technologies exhibit high efficiency in identifying new miRNAs and siRNAs.

2.3. Long Non-Coding RNAs and Potential Functions

Long non-coding RNAs (lncRNAs) are long RNA molecules present in cells that do not contribute to protein synthesis. Understanding the function of lncRNAs has been more challenging compared to messenger RNAs, which have protein-coding capabilities and contribute to protein synthesis in cells. However, recent research indicates that lncRNAs play significant roles in various cellular functions (6). The number of lncRNAs in humans exceeds the number of protein-coding genes. Advanced RNA sequencing technologies, enhanced epigenomic techniques, and recent computational methods have facilitated the discovery of more non-coding RNA transcripts, leading to an increase in the total number of lncRNAs (20).

In the last two decades, there has been a substantial increase in interest regarding the potential roles of long non-coding RNAs in regulating cellular functions. Traditionally, RNAs other than protein-coding genes were long considered 'junk RNA' and were overlooked in scientific research. However, recent studies have demonstrated that lncRNAs have various biological functions

within cells (20). lncRNAs are long RNA molecules without protein-coding capabilities, and they are believed to play significant roles in the regulation of gene expression, control of cellular functions, and the transfer of genetic information (Table 1).

Table 1. Potential Roles of lncRNAs (21, 22)

Genetic Regulators	Long non-coding RNAs (lncRNAs) can regulate gene expression by activating or suppressing various genes, potentially playing a crucial role in processes such as cell development, growth, and differentiation.
Epigenetic Control	By influencing epigenetic processes such as DNA methylation and chromatin structures, lncRNAs can regulate gene expression.
Cellular Signal Transmission	Participating in both intracellular and intercellular communication, lncRNAs can influence various cellular signaling pathways.
Interorganelle Transport	Certain lncRNAs, when transported between organelles within the cell, can effectively regulate cellular functions.

2.3.1. Types of Long Non-Coding RNAs

There are several types of lncRNAs, each with distinct functions. Firstly, there are intergenic lncRNAs, which are copied from regions between protein-coding genes. These lncRNAs often serve as a structural scaffold and guide the assembly of protein complexes to regulate gene expression (23). Secondly, intronic lncRNAs are copied from within the introns of protein-coding genes and can influence the addition or stability of the host gene's mRNA (24). Another class includes natural antisense transcripts (NATs), which are copied from the opposite strand of a protein-coding gene and can regulate gene expression through complementary base pair interactions (25). Additionally, enhancer-associated lncRNAs (Enhancer RNA) are copied from enhancer regions and can modulate the activity of nearby genes (26). Lastly, circular lncRNAs form covalently closed loops and can act as microRNA sponges or regulate protein function (27). The diversity of these lncRNA types illustrates the complexity of their regulatory roles within the cell and underscores the broader significance of understanding gene (9).

In general, lncRNAs play roles in various biological processes such as genetic labeling, chromosome organization, and allosteric control of enzyme

function. Additionally, specific lncRNA expression patterns influence overall cell state, differentiation, development, and pathology (Table 2) (22).

Table 2. Some examples of lncRNAs and their potential functions

LncRNA	Potential Function	Reference
XIST	X chromosome inactivation	28
HOTAIR	Suppresses gene expression by removing chromatin modifiers	29
TERC	Telomere extension	30
Kcnq1ot1	Regulates transcription of multiple target genes through epigenetic modifications	31
Airn	Embryonic development	32

In other words, lncRNAs can contribute to overall cellular behavior by controlling processes like apoptosis, cell death, and cell growth. Many human diseases have been associated with lncRNA gene overexpression, deficiency, or mutation. lncRNAs exhibit different expression levels across various tissues and present diverse expression patterns within different sections of the same tissue (33,34). Alterations in the expression levels of lncRNAs in various pathological conditions render them potential therapeutic targets and biomarker candidates (35).

Excessive expression of the XIST lncRNA plays a role in the development of numerous tumors. Liang et al. found that high expression of XIST in pancreatic cancer tissues and cell lines. Additionally, XIST was indicated to play a role in the cell cycle through miR-140/miR124, potentially acting as an oncogenic lncRNA supporting growth in pancreatic carcinoma (36).

In other studies, HOTAIR was identified as a trans-effect lncRNA associated with breast cancer, lung cancer, and gastric cancer (37,38). Its overexpression was reported to promote wider metastasis and stimulate cancer cell proliferation in gastric cancer tissues (39).

Studies have shown that lncRNAs play roles in cell differentiation, organogenesis, dosage compensation, and neural development. Knockdown experiments, reducing the expression of a long non-coding RNA called TUNA, have demonstrated a correlation between its expression and the severity of Huntington's disease, affecting locomotor function (40, 41).

While the role of lncRNAs in cancer is not yet fully understood, recent research indicates that these molecules may play a significant role in the

development and progression of cancer (9,42). LncRNAs can be aberrantly regulated in cancer cells, influencing the growth, spread, and development of resistance in these cells. Some lncRNAs may promote the growth of cancer cells, while others may induce cell death or inhibit cancer development (42).

Moreover, lncRNAs may be involved in epigenetic mechanisms to regulate gene expression in cancer cells. Epigenetic changes can impact gene expression without altering the DNA sequence. LncRNAs can contribute to abnormalities or corrections in gene expression in cancer cells by regulating these epigenetic changes (43,44).

However, the exact mechanisms by which lncRNAs associated with cancer function and participate in cancer processes are still under investigation. Future studies will aim to better understand the functions of cancer-associated lncRNAs and determine their potential use as new targets and biomarkers in cancer diagnosis, prognosis, and treatment.

3. Conclusion

When comparing human, and other mammalian genomes, it has been demonstrated that the degree of sequence homology outside protein-coding regions is remarkably high. To comprehensively understand the biology of higher organisms, it is crucial not only to grasp the proteomes but also to identify non-coding RNAs, elucidating their expression patterns, processing, and signaling pathways. The identification of non-coding RNA defects in human diseases increases promising prospects in the therapeutic field. It is clear that future research will uncover different treatment approaches associated with non-coding RNAs, guiding the development of therapies based on newly revealed information.

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CHAPTER III

MULTIPLE SCLEROSIS AND MICRORIBONUCLEIC ACIDS

Orcun AVSAR

(Assist. Prof. Dr.), Hitit University,
Faculty of Arts and Sciences, Department of
Molecular Biology and Genetics
E-mail: orcunavsar@hitit.edu.tr
ORCID: 0000-0003-3556-6218

1. Introduction

Multiple sclerosis (MS) is an inflammatory and autoimmune neurodegenerative disease and it has an impact on the central nervous system. The destruction of the myelin sheath - a structure that surrounds and protects nerve cells - is a characteristic feature of the disease. This damage causes MS symptoms by slowing or blocking the transmission of nerve impulses between the brain and the body. The disease demyelinises central nervous system axons, leading to loss and atrophy of nerve cells in the spinal cord and brain. The aetiology of multiple sclerosis is unclear and the diagnosis of the disease is mainly based on symptoms and lacks an effective laboratory test index. Recent scientific data supports that miRNA dysregulation is associated with neurodegenerative diseases such as MS, and miRNAs are considered to have the potential for use as diagnostic markers and therapeutic targets in MS.

2. Multiple Sclerosis

Multiple sclerosis (MS) is a multifactorial neurological disease characterised by multifocal inflammatory lesions which cause damage to the myelin sheath and axonal degeneration, affecting the spinal cord and the brain. The disease

is characterised by destroying the myelin sheath, the structure that surrounds and protects nerve cells, axonal injury, glial hyperplasia, and inflammation (1). This damage causes MS symptoms by slowing or blocking messages between the body and the brain. Women have twice the chance of getting MS than men, and the disease usually begins between the ages of 20 and 50. In 2015, about 2.3 million people worldwide were affected by the disease, and about 18,900 people died from MS in the same year (2).

There are four different clinical types of MS: Relapsing-remitting MS, primary progressive MS, relapsing-remitting progressive MS and secondary progressive MS. The most common type of MS is known as relapsing-remitting MS, occurring in 85% of cases. While relapsing-remitting MS is associated with focal demyelination, axonal degeneration and neuronal loss are observed in progressive forms of the disease (3).

MS disease has been shown to result from the infiltration of activated immune cells into the central nervous system during an immune-mediated inflammatory response, but the aetiology is not fully understood (1,3). Although the mechanism of the disease is still a mystery, it is generally recognised as an autoimmune attack on the myelin sheath mediated by humoral and cellular immunity (4). MS determines gene expression as a result of a complex interaction between genetic, epigenetic and environmental factors, but the molecular mechanisms underlying this interaction are not fully understood (5). Vitamin D deficiency, miRNA dysregulations, Epstein-Barr virus infection, stress, childhood obesity, DNA methylation, and smoking are some of the environmental factors identified in MS, which is a multifactorial disease (Figure 1). These factors are thought to affect processes such as the differentiation, proliferation, and apoptosis of cells and are associated with miRNAs (6). For the progressive form of MS, there is currently no effective treatment. This is partly due to a lack of sensitivity in the measurement of neurodegeneration (7).

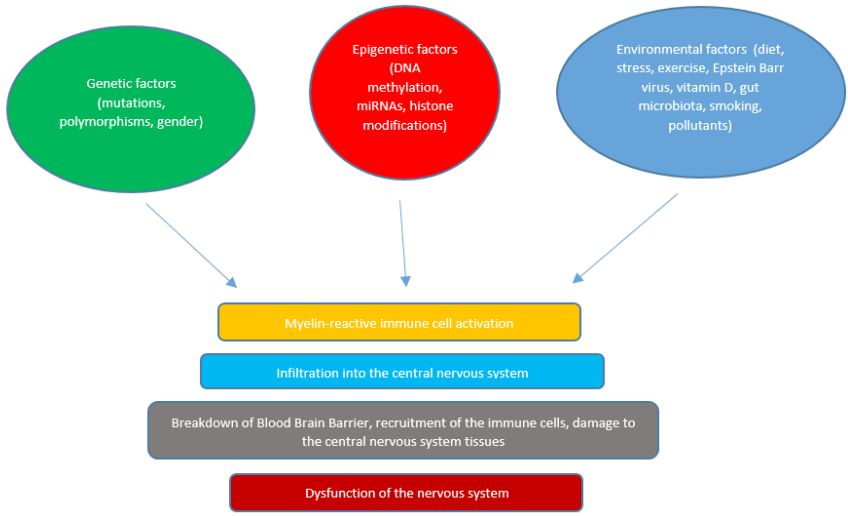

Figure 1. Pathogenesis of MS and risk factors.

3. MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are endogenous and small non-coding regulatory RNA molecules that suppress the expression of genes that are involved in a variety of biological processes. The vast majority of miRNAs are transcribed from DNA sequences to form primary miRNAs. Canonical and non-canonical pathways are involved in miRNA biogenesis (Figure 2) (8). miRNAs are single-stranded molecules of 17-22 nucleotides and are post-transcriptional regulators. In other words, they regulate the expression of genes and proteins. In general, they destabilise mRNAs and suppress translation by recognising target sequences in the 3'UTR (untranslated region). In short, miRNAs either suppress gene expression by fragmenting the target mRNA or inhibit protein expression by repressing translation (9). Since miRNAs can cross the blood-brain barrier (BBB), they may also be detected in the brain circulation. In short, miRNAs are thought to be found in various biological fluids such as cerebrospinal fluid (CSF), plasma, serum and interstitial fluid, and to play a role in intercellular communication (Figure 3) (10). miRNA molecules are highly resistant to conditions such as RNase degradation, high pH and boiling due to their high stability (2).

MicroRNA molecules are known to participate in a wide range of biological processes such as neurodegeneration, immunity, inflammation, regulation of the immune system and lipid metabolism (Figure 4). It's thought that miRNAs are involved in causing diseases such as MS, cancer, Parkinson's and Alzheimer's, and can be used in disease screening (11).

4. MicroRNAs: Potential Diagnostic Biomarkers in Multiple Sclerosis

Multiple sclerosis is diagnosed according to the clinical presentation of patients, physical examination, blood tests, examination of the cerebrospinal fluid, electrophysiology, and magnetic resonance imaging. The variability of symptoms and signs in people with MS affects the diagnosis of the disease and leads to a high risk of misdiagnosis (12, 13). More recently, miRNAs have been shown to be potential biomarkers for various diseases such as multiple sclerosis. Alterations in the function and composition of miRNA present in the biological fluids of individuals with MS are being studied as potential accurate markers of MS activity (14).

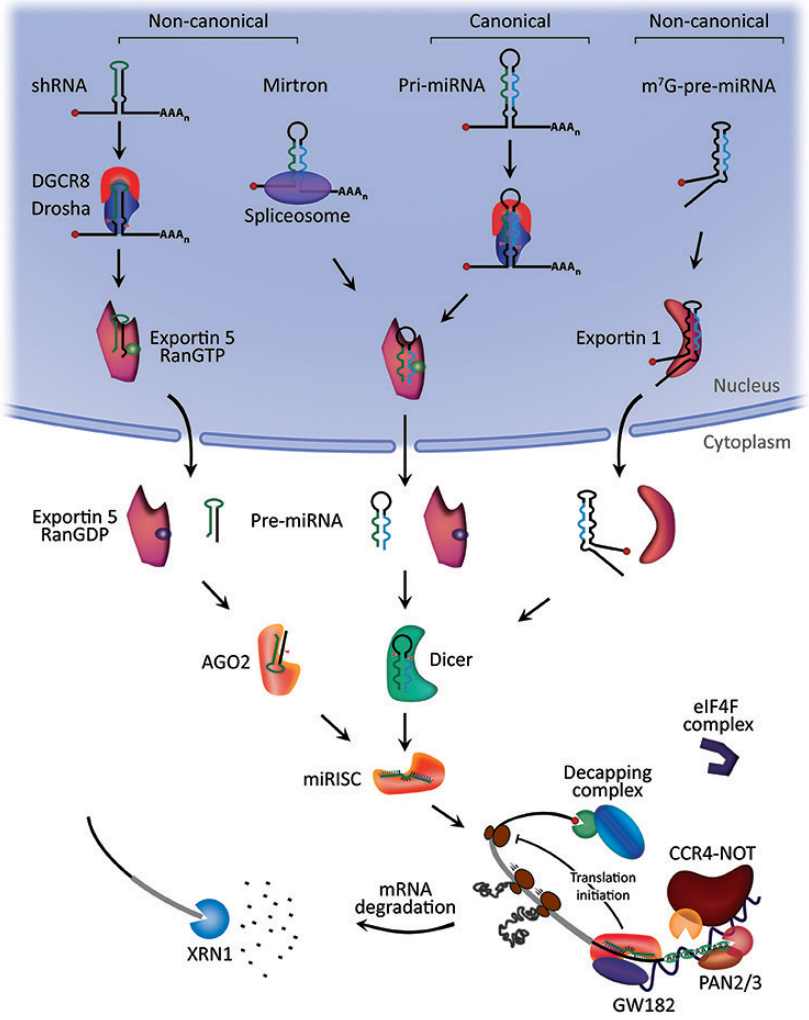

Figure 2. The biogenesis of microRNA molecules and the mechanisms of their action (8).

The dysregulated expression profiles of miRNAs can lead to the alteration of a range of biological processes such as proliferation, differentiation and apoptosis and then dysfunction of mainly immune cells, which are implicated in the development and progression of multiple sclerosis (15). In multiple sclerosis, the expression levels of many miRNAs have been shown to be altered in exosomes and various biofluids such as cerebrospinal fluid, serum and peripheral blood, and can discriminate between disease phenotypes and may be useful in distinguishing between subtypes of MS (13). Some microRNAs may be candidates for biomarkers that may indicate the onset of remyelination, the degree of neurodegenerative damage, or the generation and deterioration of immune and CNS cells and molecules that may help to diagnose and differentiate the types and the stages of MS in patients (15,16). In contrast, studies in the literature show that the diagnostic value of microRNAs is still a matter of controversy. Therefore, further studies are needed to independently confirm these results from different studies, thus single or panels of miRNAs in peripheral blood or CSF may have the potential to be used as potential diagnostic markers for both paediatric and adult MS.

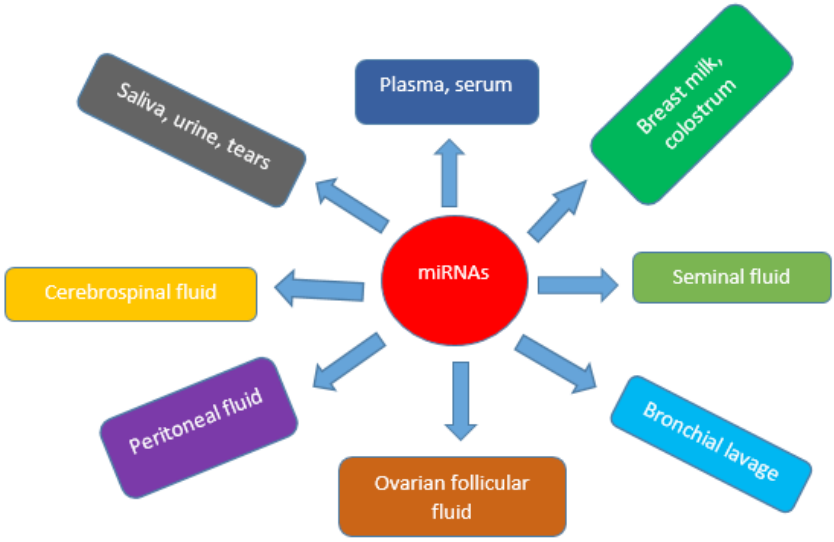

Figure 3. miRNA molecules in biological fluids.

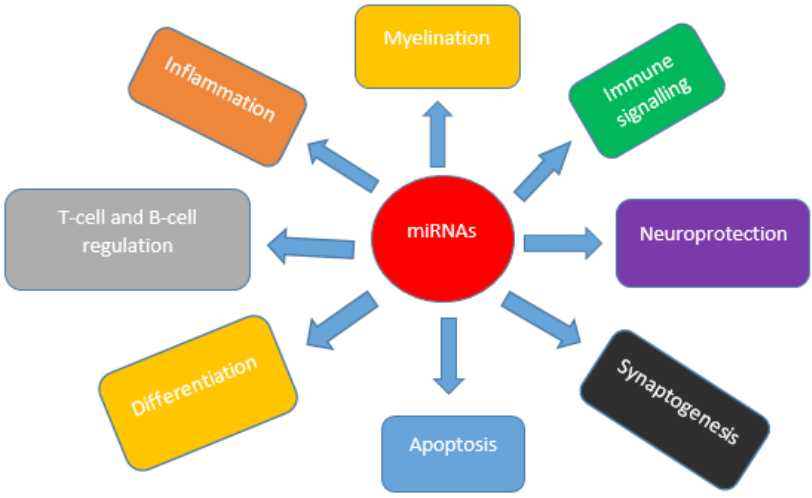

Figure 4. miRNA functions in the central nervous system.

5. Therapeutic Potential of miRNAs in the Treatment of Multiple Sclerosis

Available treatments for MS concentrate on reducing immune activity and infiltration, resulting in less inflammatory damage to the central nervous system. Hence, they are mainly effective in relapsing-remitting MS. On the other hand, there is a relative lack of treatment options that target the more advanced stages of the disease and concentrate on the repair of the damaged lesions (17).

The myelin sheath in the CNS is produced by oligodendrocytes and recruitment of oligodendrocyte precursor cells (OPCs) to damaged regions and their desired differentiation are critical for repair in MS. This biological process is modulated by numerous factors such as miRNAs, cytokines, neurotransmitters, and chemokines (17, 18,19).

Through modulation of the pharmacokinetics and pharmacodynamics, or by having an impact on the pathological process itself, miRNAs can have a major impact on drug response. The epigenetic modulation of drug transporters, such as SLC and ABC transporters, and genes that are involved in the expression of the drug metabolising enzymes, such as cytochrome P450s (CYP450s), are influenced by many miRNA molecules (20,21). In addition, miRNA polymorphisms, or miRSNPs, play a crutial role in the regulation of genes. A large number of polymorphisms in miRNAs have emerged as potential prognostic biomarkers and therapeutic modifiers (22).

Antisense oligonucleotides (anti-miRNAs) have the potential to be used to inhibit specific miRNAs to prevent the abnormal expression levels of target genes, known as RNA silencing, which is implicated in numerous biological signalling pathways related to MS (23). In addition, miRNAs can be used to assess and monitor the efficacy of MS treatment. The potential of new drugs such as natalizumab can be further evaluated by using miRNAs as biomarkers (24).

miRNAs are a promising research tool for the development of novel therapeutics aimed at restoring remyelination in MS. The use of high-throughput techniques in modern and molecular medicine such as stem cell transplantation, nanomedicine, and gene therapy may contribute to the potential applications of miRNAs in the treatment of MS.

6. Conclusion

There is a need to identify new biomarkers that can be used in the diagnosis and treatment of MS. MS is diagnosed using the McDonald criteria, that are considered to be the gold standard. In some cases, the McDonald criteria are not sufficient to make a diagnosis in some patients with mild symptoms. However, long-term outcomes are better the earlier the diagnosis and intervention. In this context, it is very important for MS to identify miRNA molecules in different biological fluids such as blood, which can potentially be used in the clinic for early diagnosis of MS and monitoring of treatment response. In short, identifying miRNA profiles in fluids such as blood is very important in determining individuals susceptible to MS disease, disease severity and treatment response, and is also promising in terms of disease management. The identification of miRNAs in various biofluids such as blood and cerebrospinal fluid is also very important for understanding MS disease at the molecular level, for early diagnosis and for monitoring treatment response. Many new studies are needed because many miRNAs have been identified and there are differences in the changes in miRNA expression levels between studies. In addition, because ethnicity is important, miRNA analyses need to be performed in different populations. Further research using modern statistical and technological approaches is required to identify new and useful biomarker tools for the diagnosis and prognosis of multiple sclerosis.. For the development of novel therapeutics aimed at restoring remyelination in MS, miRNAs are a promising avenue of research.

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CHAPTER IV

PHARMACOGENETICS AND CLINICAL APPLICATIONS

Şebnem YILDIRIMCAN KADIÇEŞME

(Asst. Prof. Dr.), Kafkas University, Faculty of Medicine, Department of Medical Biology, Kars, Turkey.
E-mail: sebnem.yildirimcan@kafkas@edu.tr
ORCID: 0000-0002-8908-9464

1. Introduction

Today, a trial-and-error approach is used in the treatment of diseases. In this method, standard treatment protocols are applied to each patient, and the treatment is modified in case the patient does not improve or experiences side effects. (1)

Prescribed medications are not effective in about 50% of patients. Despite prescribing the same treatment for patients with the same diagnosis, some may show improvement, while others may not respond to treatment, and some may experience side effects. The reason for this is interpersonal differences. Factors such as age, race, gender, environment, diet, and drug interactions lead individuals to respond differently to medications. (2)

Recent studies have shown that, in addition to these reasons, genomic differences among individuals also play a significant role in response variations to drugs. Genetic factors influence the elimination rate of drugs, as well as the quality and quantity of drug receptors and other structures in target cells, contributing to variability in drug effects among individuals, ethnic groups, and races. Instead of traditional treatment methods, determining the genetic profile of patients and providing personalized treatments based on this information will enhance treatment effectiveness. Pharmacogenetics is one of the crucial applications of personalized medicine. (2,3)

2. Basic Concepts in Pharmacogenetics

Drugs interact with various proteins in the body from ingestion until elimination. There are individual differences in the proteins that the drug molecule interacts with. Polymorphisms in the genes that synthesize these proteins lead to interindividual differences in drug responses. (4)

Polymorphism is a genetic variation found in more than 1% of the population. Polymorphisms (variations) lead to differences in drug responses by causing changes in the structure and synthesis of proteins (such as receptors and transporter proteins) involved in absorption, distribution, metabolism, clearance, excretion, and target structures. They can alter drug efficacy and contribute to the emergence of drug-related side effects. (4,5) Information about the impact of genetic polymorphisms on drug responses can be accessed from databases such as PharmGKB, dbSNP, and GWAS Central. (6)

There are four main types of polymorphisms: restriction fragment length polymorphisms (RFLP), variable number tandem repeats (VNTR), short tandem repeats (STR) and single-nucleotide polymorphisms (SNPs). The most prevalent kind of polymorphism seen in humans is SNPs. (5)

A single nucleotide's (DNA building block) change is represented by each SNP. For instance, in a particular DNA sequence, an SNP can convert the nucleotide cytosine (C) to thymine (T). SNPs are naturally present in a person's DNA. On average, they occur nearly once in every 1,000 nucleotides, meaning there are roughly 4 to 5 million SNPs in a person's genome. These variations are seen in many individuals, and for a variant to be classified as an SNP, it needs to be present in at least 1% of the population. Scientists have identified over 600 million SNPs in populations worldwide. (4,7)

Due to genetic variations observed among individuals, only 20-40% of patients may benefit from the prescribed medication, and 70-80% of candidate drugs fail in clinical trials. Additionally, many approved drugs are withdrawn from the market due to side effects. (8)

Pharmacogenetics is the branch of science that examines the response of individuals to drug metabolism depending on the variability in their genetic structure and the different effects that may occur on the individual. (9)

Pharmacogenetic studies, which began in the second half of the last century, have gained significant importance in the past 20 years. Following the identification of the entire human genome sequence in the early 2000s, studies on the relationship between variations in multiple gene regions and drug efficacy and toxicity have accelerated, thanks to whole-genome sequencing technology.

As a result, the more comprehensive term "pharmacogenomics" started to be used. The terms pharmacogenetics and pharmacogenomics are often used interchangeably and synonymously. The science of pharmacogenetics aims to achieve maximum treatment response with minimum drug side effects by applying the most suitable drug at the optimal dose based on an individual's pharmacogenetic profile. The main objective of the field of pharmacogenomics is to identify the genetic infrastructure underlying the differences in response between individuals and to ensure that genetic tests can be used for effective and safe treatment. (8,9) In short, pharmacogenetics is a subfield of pharmacogenomics.

In pharmacogenetic and pharmacogenomic studies, genetic variations are associated with pharmacokinetics (examining the effects of the body on the drug), pharmacodynamics (studying the effects of the drug in the body), and/or immunogenicity. As a result, the effects of genetic changes (acquired or hereditary) on drug responses in patients are evaluated. (9)

Every day, millions of people around the world use medicines that are not effective in their treatment or have side effects in the hope of getting better. For example, it has been estimated that 1/4 to 1/25 of the most commonly used drugs in the United States are effective in treatment. In the case of statin drugs used to lower cholesterol levels, the therapeutic effect can drop to 1/50. (10) In the United States, approximately 7% of hospital admissions each year are due to drug-related side effects. The toxic effects of medicines cause around 100,000 deaths annually. (10) Pharmacogenetics-based personalized treatments stand out as one of the most crucial applications to overcome these problems.

3. Clinical Applications of Pharmacogenetics

Clinical studies related to pharmacogenetics and pharmacogenomics began in the late 1960s and have experienced significant acceleration in the last 20 years.

Pharmacogenetic studies have two main clinical applications: 1. distinguishing patients who respond well or poorly to a drug. 2. identifying patients who may experience side effects and toxicity. For this purpose, laboratory tests such as therapeutic drug monitoring (TDM) and genetic profiling tests for the drugs used are conducted. (11)

When determining the patient's pharmacogenetic profile, the following steps are taken: 1. DNA analysis (genotyping) is performed. 2. Genetic

polymorphism is preliminary diagnosed through TDM. 3. Phenotyping is carried out using a 'probe drug' (a measuring substance). (11)

The significance of pharmacogenetic tests can be explained as follows: If a genetic test is conducted on an individual, the drug dosage is personalized before side effects occur at the prescription stage. If the individual has not been genetically tested, a person who metabolises the drug slowly will be prescribed a standard dose, side effects will occur (toxic dose of the drug), the patient will consult the doctor again and the dose will be adjusted again. If the person metabolises the drug rapidly, the drug will never reach the normal blood level because the drugs are broken down very quickly, the disease will continue with the same severity as if the patient is not receiving any treatment, or even progress. (11)

Pharmacogenetic testing allows us to optimize and individualize treatment for each patient in the light of genetic information. It is possible to apply the most effective, appropriately dosed, and minimally side-effect-prone treatments through personalized and individualized treatment approaches for each patient. (11)

As our knowledge of how genetic variants impact pharmacological responses has grown, so too has the significance of DNA-based diagnostic techniques that forecast medication reactions and adverse effects. The first Food and Drug Administration (FDA)-approved pharmacogenetic test (2004), the AmpliChip CYP450 Test, is a clinical test developed by the Roche company. (12)

Cytochrome P450 enzymes (CYP450) are responsible for the biotransformation of many drugs used in clinical practice. (12) CYP450 enzyme functional differences due to individual genetic variations result in individuals metabolizing drugs to varying degrees, leading to different drug levels in the bloodstream. Changes in drug blood levels can result in drugs either not reaching therapeutic doses or reaching toxic levels. Functional polymorphisms in genes coding for CYP450 enzymes can lead to a lack of drug response or drug toxicity. Patients are classified into four categories based on the working speed of CYP450 enzymes: 1. Poor Metabolizers (Enzyme does not work) 2. Intermediate Metabolizers (the enzyme works slowly) 3. Rapid Metabolizers (the enzyme works at a normal speed) 4. Ultrarapid Metabolizers (the enzyme works very quickly). (12,13)

In order to prevent deaths due to drug dosage errors, the CYPP450 enzyme activities of humans should be measured in a practical way, and drug

dosages should be made accordingly. The genetic structures of people should be analyzed, drug dosages should be adjusted according to the structures of the existing genes, and personalized treatment should be performed. (12)

The AmpliChip CYP450 Test was developed to identify polymorphisms in two CYP450 enzymes (CYP2D6 and CYP2D19), which allows one to assess a person's capacity to metabolize specific drugs. This test is intended for use in the clinic for treatment selection and individualisation of treatment dose. This test, which is used especially for psychiatric patients, uses Microarray technology. DNA for the test is extracted from blood or cheek epithelium. (13)

Awareness of the importance of pharmacogenetics in the field of healthcare is steadily increasing. However, the practical application of pharmacogenomics is time-consuming due to various factors. Ordering pharmacogenetic testing when prescribing medicines in the clinic is not only costly but also time-consuming. Instead of gene-based tests, comprehensive pharmacogenetic screenings containing numerous genes would be more advantageous for routine use. Large-scale studies on the use of pharmacogenetic data in individualised treatment are important for this application to enter routine clinical practice. In this context, the PREPARE (Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions) study is the largest prospective clinical research conducted in Europe. (1)

This study documented the benefits of conducting pharmacogenetic tests before starting drug therapy. Participants were recruited from various centers in seven European countries (Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK). The study showed that genotype-guided therapy using a 12-gene pharmacogenetic panel significantly reduced the frequency of clinically relevant adverse drug reactions. Comprehensive research could help make drug treatment increasingly safe. (14)

Four major study groups that create guidelines regarding the use of pharmacogenetic data in drug applications are the Dutch Pharmacogenetics Working Group, the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety, and the French National Pharmacogenetics Network. Recommendations from these groups, along with evidence levels of drug-gene interactions and pharmacogenetic test-related information on product labels, can be accessed through https://www.pharmgkb.org. The open accessibility of these data has been extremely effective in the dissemination of pharmacogenetics. However, it is crucial to use the obtained information ethically and in

compliance with ethical and legal standards to avoid violating individuals' rights. (1,10)

Doctors benefit from the guidelines published by these groups to ensure that patients receive the correct medication at the right dosage. Important pharmacogenomic markers that impact the efficacy and safety of drugs are also included in drug information documents. Currently, the FDA is requesting the inclusion of pharmacogenomic information and biomarkers for dozens of drugs in drug documents. Related medicines are listed by the FDA. (15) Some of these drugs and the pharmacogenomic information requested are provided in Table 1. (16)

Table 1. Examples of Drugs for Which Pharmacogenomic Information is Requested in FDA Drug Documents (16)

Drug	Therapeutic area	Biomarker	Pharmacogenomic Information in the Medication Document
Abacavir	Infectious Diseases	HLA-B	High risk in terms of hypersensitivity reactions in individuals carrying the HLA-B*5701 allele
Aripiprazole	Psychiatry	CYP2D6	Dose determination in CYP2D6 slow-metabolizer individuals
Flurbiprofen	Rheumatology	CYP2C9	Dose restriction in CYP2C9 slow-metabolizer individuals
Clopidogrel	Cardiology	CYP2C1	Use of blockers another P2Y12 receptor in CYP2C19 slow metaboliser individuals
Codeine	Anesthesiology	CYP2D6	Warning against severe respiratory impairment in CYP2D6 ultrarapid metabolizer children
Mercaptopurine	Oncology	TPMT	Increased risk of toxicity in individuals with low TPMT activity
Warfarin	Hematology	CYP2C9 VKORC1	Dose determination according to the CYP2C9 and VKORC1 genotypes
Ivacafftor	Pulmonary	CFTR	Before beginning treatment, the patient's CFTR genotype was determined using bidirectional sequencing

For example, codeine, belonging to the class of opioid analgesics, is used in the treatment of mild to moderate pain (Table 1). Morphine, the metabolism

product of codeine, shows its effect by binding to the opioid receptor. The enzyme CYP2D6, which is part of the cytochrome P450 family, catalyzes the conversion of codeine to morphine. In individuals with two inactive copies of CYP2D6 ("poor metabolisers", PMs), pain cannot be adequately treated due to reduced morphine levels. Individuals carrying more than two functional copies of the CYP2D6 gene ('ultrarapid metabolizers,' UMs) can metabolize codeine faster and more completely. In these individuals, symptoms of morphine overdose, such as drowsiness, confusion, respiratory failure, etc., may occur. CPIC recommends using an alternative analgesic instead of codeine if an individual is an ultrarapid metabolizer for CYP2D6. Additionally, CPIC does not recommend the use of codeine in individuals who are poor metabolizers for CYP2D6 due to inadequate efficacy. (17)

Warfarin, another drug for which pharmacogenomic information is requested in FDA drug documents, belongs to the anticoagulant drug class. If not administered at the correct dosage, warfarin can pose a significant risk to the patient's life due to potential bleeding disorders. Therefore, the FDA recommends determining the appropriate dose based on an individual's genotype before administering this drug. (18,19)

Warfarin's target protein is vitamin K epoxide reductase complex subunit-1 (VKORC1). VKORC1 ensures the conversion of vitamin K epoxide, which is involved in the activation of clotting factors, to reduced vitamin K. Warfarin reduces the amount of reduced vitamin K by inhibiting the vitamin K epoxide reductase enzyme. As a result, it exhibits anticoagulant effects by inhibiting the activation of clotting factors (II, VII, IX, and X). (18)

VKORC1 gene polymorphisms have been linked to warfarin resistance, a condition in which people need larger doses of warfarin than recommended. Due to polymorphisms in the *VKORC1* gene, Warfarin cannot bind sufficiently to VKORC1, requiring higher doses of Warfarin. If individuals with these polymorphisms receive normal doses of Warfarin during anticoagulant treatments, there is a risk of developing harmful blood clots. (18,19)

Furthermore, variations in the *VKORC1* gene have been linked to warfarin sensitivity, a disorder in which people need smaller doses of warfarin than recommended. The most common polymorphism in these individuals is VKORC1A. As a result of this polymorphism, VKORC1 levels decrease, leading to warfarin sensitivity, and lower doses of warfarin are needed. Individuals with warfarin sensitivity are at risk of overdosing if they take doses above average. Overdose can result in life-threatening bleeding disorders in the brain,

gastrointestinal system, or other tissues. Polymorphisms in the *CYP2C9* gene, in addition to the *VKORC1* gene, also contribute to warfarin sensitivity. (10)

Pharmacogenetics plays a significant role in planning cancer treatments, and one of the best examples of its use in oncology is the US National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, initiated in 2015. This study is a clinical investigation aiming to determine the effectiveness of treatment when specific genetic alterations are present in the patient's tumor. Screening and molecular tests were conducted on approximately 6,000 patients. The study included drugs approved by the FDA for other cancers or drugs in clinical trials that are effective in treating tumors with certain genetic alterations. (20)

The research included individuals with advanced-stage solid tumors, lymphoma, or myeloma, as well as those with rare cancers. The NCI-MATCH clinical trial comprises 38 treatment arms, each targeting a gene abnormality triggering the carcinogenesis process. Table 2 provides some of the molecular targets and related drugs in these treatment arms. (21)

Table 2: Molecular Targets and Related Drugs within the Scope of the NCI-MATCH Study (21)

DRUGS	CANCER TYPE	GENOMIC TARGET(S)
Crizotinib	Non-small cell lung cancer	*ALK* rearrangements
Crizotinib	Non-small cell lung cancer	*ROS1* rearrangements
Trametinib	Melanoma	*BRAF* fusions or non-*V600E, non-V600K BRAF* mutations
AZD4547	Squamous cell lung cancer, gastric cancer, bladder cancer, hormone receptor–positive breast cancer	*FGFR* pathway aberrations
Binimetinib	Solid tumor, lymphoma, or multiple myeloma	*NRAS* mutations
Copanlisib	Solid tumor or myeloma	*PIK3CA* mutation with or without PTEN loss
Taselisib	Solid tumors other than breast and squamous lung cancer	*PIK3CA* mutation without *RAS* mutation or *PTEN* loss

The study closed patient enrollment on December 23, 2022. NCI-MATCH results have demonstrated the utility of genomic sequencing in planning the treatment of advanced-stage cancer patients. Patients participating in the study

will continue to be monitored for an additional 3 years after treatment. Articles related to the obtained data are still being published.(22)

4. Conclusion

The increased accessibility of genetic tests thanks to technological advancements, increasing studies in the field of pharmacogenetics and the accumulating knowledge, will enable personalized treatment for numerous drugs.

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CHAPTER V

BIOMINIMALISM IN CONTEMPORARY ENDODONTICS

Tugba TURK

(Prof.Dr.), Ege University, School of Dentistry Department of Endodontics
E-mail: btugbaturk@gmail.com
ORCID: 0000-0002-3726-3715

1. Introduction

In recent years, technological advancements in fields such as cell biology, bioengineering, nanotechnology, robotic technology, and high-resolution imaging systems, among others, have enabled the adoption of minimally invasive treatments across diverse medical fields. Minimalism is a design and lifestyle philosophy focused on simplicity, a few elements, and effective functionality. (1) The core idea of minimalism is to eliminate unnecessary elements and clutter, leaving only what is effective and meaningful. With the concept that 'less is more,' there emerges a sense of great clarity and meaning, valuing quality over quantity and finding functionality in simplicity.

Biominimalism in endodontics represents two critical principles: minimalism and biological approaches. While minimalism involves simplifying treatment processes by reducing unnecessary interventions, biological approaches focus on harnessing the body's innate regenerative potential. This new synthesis, termed "biominimalism," aims to revolutionize endodontic treatments by combining procedures that are both compatible with each patient's biological nature and simplified. At its core, biominimalism emphasizes more biologically personalized strategies. The goal is to support the cellular function of natural tissues by using biomaterials that harmonize with the body's natural healing processes as much as possible, ensuring both aesthetic and functional continuity. The concept of minimally invasive endodontics necessitates treating pulp-dentin and apical pathologies with minimal alterations to dental tissues.

The objective of this approach is to preserve the durability and function of an endodontically treated tooth while ensuring its functionality throughout the patient's lifetime. Thanks to recent technologies, biominimal principles can easily adapt to both conventional and regenerative endodontic treatments.

2. Biominimal Approaches in Conventional Endodontic Treatment

The primary goal of conventional endodontic treatments is to prevent the formation of apical periodontitis or treat it if already present, ensuring the long-term functionality of the tooth. However, several factors influence the outcomes of endodontic treatments. For instance, factors like restoration quality and the structural integrity of the tooth after chemo-mechanical cleaning of the root canals play a pivotal role. A modern approach in conventional endodontics, at its simplest form, aims to minimize structural losses during root canal treatment. This approach has been termed and defined as "minimal invasive endodontics". (2) The concept of minimal invasive endodontics involves treating and preventing pulpal pathologies and apical periodontitis with minimal alterations to dental tissues. (3) Like in other fields, endodontists need to employ the latest technology, materials, and methods to perform minimally invasive procedures. Imaging systems, magnification systems, computer software, new methods, and materials for canal disinfection, biomaterials, and next-generation restoration techniques significantly contribute to this regard. (2,3)

The remaining structural integrity of an endodontically treated tooth is a crucial factor determining the prognosis of the tooth after restoration. (4,5) Preserving the tooth's resilience and resistance to structural deformation is a primary objective, especially in restorative treatments following endodontic therapy The intricate anatomy of root canals can pose significant challenges during endodontic treatment. In classical endodontic treatment, the primary focus lies in accessing the root canal system effectively for thorough cleaning and filling. Older classical endodontic references suggest direct and linear access to root canal orifices from the occlusal surface, recommending that the access cavities be widened larger towards the occlusal direction. However, with advanced magnification systems and modern root canal instruments, this approach has been abandoned. (6,7) Furthermore, recent insights suggest the criticality of peri-cervical dentin for the long-term survival and optimal functions of a tooth, emphasizing the importance of preserving its structural integrity. (7)

In endodontic treatment, the complete removal of microorganisms from the root canal system is the primary goal. (8) At first glance, any minimally invasive approach to root canal treatment might seem contradictory to disinfection, but this contradiction has not been conclusively proven in the literature. (9) Classical disinfection and shaping methods have not been able to completely eliminate the microbial load from the root canal system, leading to ongoing research efforts to find more effective and convenient disinfection methods. Ongoing studies on new physical methods, activation systems, laser systems, and nanomolecules are showing promising results. (10,11)

Long-term success is undeniably crucial in endodontic treatments, not only addressing acute symptoms but ensuring sustained effectiveness. Even if the endodontic procedure is successful, having to extract the affected tooth due to reasons like fractures is not an acceptable outcome for patients and can be directly perceived as a failure of the endodontic procedure. (12) Studies about the restoration of endodontically treated teeth emphasize the vital significance of preserving the integrity of both coronal and radicular tooth structures by providing a 'ferrule effect' in peri-cervical tissues. (13) The integrity of the remaining dentin walls provides a protective effect by reducing internal stresses within the tooth. Having a 1.5-2 mm ferrule in the coronal region significantly impacts the fracture resistance of endodontically treated teeth. (13)

The main focus of conventional biological endodontic treatment involves preserving the remaining tissues by minimizing the removal of dental tissues, disinfecting the remaining tissues using advanced irrigation techniques, and filling the root canals with biomaterial-based filling materials (13). Simultaneously, the coronal restoration should possess biomimetic properties.

3. Vital Pulp Treatments

Pulp preserving treatments aimed at preserving pulp vitality, which constitute a true biominimal endodontic approach, have been among the most doubted endodontic treatments since the inception of the focal infection theory in the early 1900s. However, current evidence suggests that most pulpal infections and inflammations in permanent teeth can be managed. It has been proven that inflamed pulp tissue, previously considered 'irreversible,' possesses the ability to heal. (14,15) Recent statements from the American Association of Endodontists and the European Society of Endodontology underline that the absolute treatment for irreversible pulpitis does not necessarily involve

pulp extirpation. (16,17) This development marks the beginning of a new era for biologically minimally invasive endodontic treatments and is considered a significant step toward emphasizing a treatment approach with minimal interference with natural tissue. The shift in the current paradigm indicates that dentists should also consider pulpotomy as a definitive treatment method for cases diagnosed with irreversible pulpitis or deep decay.

In the past, pulp tissue was believed to be entirely defenseless against bacterial attacks. It was thought that when microorganisms accumulated due to factors like decay, the infection would rapidly progress throughout the entire root. There was a prevalent belief that the narrow apical opening of mature teeth, wouldn't suffice for cellular defense. Hence, any inflammation within the pulp tissue was considered irreversible. Despite the disadvantage of being enclosed within dentin walls without collateral circulation, studies have shown that pulp tissue can tolerate moderate pressure increases during inflammation and possess an effective defense system (18,19). Presently, the pathophysiology of pulp tissue, its defense mechanisms, and its healing capacity have been elucidated at the cellular level. (18)

Histological studies have revealed that in teeth with irreversible pulpitis or with an exposed pulp due to decay, there exists a necrotic area colonized by bacteria within the pulp. (20) However, a few millimeters away from the area colonized by bacteria, there is often healthy pulp tissue free from inflammation and bacteria. (21) Within pulp tissue, there exist innate and adaptive immunological mechanisms against bacterial infections. (22,23) If no treatment is applied to eliminate microbial accumulation, the inflamed pulp area can gradually enlarge and spread to other areas of the pulp, yet healthy pulp tissue not infected in the root region can still be present. (20) Theoretically, when the infected portion of the pulp is completely removed, active immune/inflammatory cells in the area become deactivated through apoptosis and are removed from the environment, creating a conducive environment for the healing of the remaining pulp tissue. Subsequently, odontoblast-like cells differentiated from odontoblasts or stem cells begin to secrete dentin.(22) Considering all these mechanisms, the presence of severe inflammatory cells histologically within the pulp does not imply irreversibility for the entire pulp tissue.

Therefore, it is now acknowledged that the presence of inflammation in the pulp does not necessarily signify irreversible total necrosis. Instead, inflammation is recognized as a desired defense mechanism and is known to initiate repair and healing in the pulp when the appropriate conditions are. (21)

However, if pulpal inflammation persists continuously and uncontrolled without necessary treatments applied to the tooth, the inflammation spreads throughout the entire pulp tissue, potentially leading to total necrosis.

4. Pulp Revitalization

Regenerative endodontic treatment is defined as biologically based procedures that facilitate the cellular repair of damaged tissues, encompassing dentin, pulp, cementum, and periodontal tissues. (24-26) Various terms such as regeneration, revitalization, and revascularization have been used to describe this procedure. (27) Resolving clinical signs and symptoms, completing root development, and re-establishing neurogenic structures are among the goals of regenerative endodontic treatment. (28)

The foundational principles of regenerative endodontic treatment in devitalized teeth were established through Nygaard-Ostby's experimental studies. (29). Nygaard-Ostby emphasized the significance of induced bleeding at the apex and the formation of a blood clot within the canal. Subsequently, Iwaya et al. published a similar treatment method called revascularization for immature non-vital permanent teeth in 2001. (30) Their treatments not only eliminated clinical and radiological symptoms but also induced the thickening of the canal walls and closure of the wide apical opening in immature permanent teeth. In later years, as it became evident that the regenerated tissues encompassed not only blood vessels but also hard and soft tissue gains, the use of the term "revitalization" was proposed instead of "revascularization". (31) The American Association of Endodontists acknowledged and endorsed the term 'regenerative endodontics' in 2007 as a treatment based on tissue engineering concepts. (26) Likewise, in 2016, the European Society of Endodontology issued detailed treatment guidelines. (32)

Regenerative endodontics relies on three fundamental components: stem cells, scaffolds, and bioactive growth factors. (28,33) There are two primary tissue engineering strategies used to form the pulp-dentin complex: placing stem cells into the region (cell-based) or recruiting stem cells to the area (cell homing). (28,34) Despite its initial application primarily in immature teeth, recent debates and numerous publications have emerged regarding the viability of regenerative endodontic treatment in mature teeth. (27,35) In mature and immature devitalized teeth, filling the root canal space with biological tissues containing similar cells, blood vessels, and nerve structures rather than synthetic materials represents a truly biomimetic endodontic

approach. Creating an environment conducive to new tissue formation through minimal canal enlargement for maximum disinfection and harnessing the natural reserves of the tissue is now achievable with modern materials and techniques.

Advanced clinical and laboratory studies conducted and anticipated in this field suggest a potential for further enhancement in success rates in the future.

5. Conclusion

The contemporary approach in endodontics integrates the preservation of natural tissues, addressing pulp and dentin pathologies through a blend of biological and minimal treatment methods. Biominimalism, a convergence of minimalism and biological approaches, personalizes treatments and embodies biomimetic attributes. Minimally invasive principles, actively bolster the body's natural healing mechanisms. These adaptable principles are versatile for both conventional and regenerative endodontic treatments, potentially elevating their effectiveness and improving patient comfort. Looking ahead, the introduction of advanced bio/materials into endodontic treatments will enhance the predictability and popularity of biominimal approaches.

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CHAPTER VI

ORAL HEALTH MANAGEMENT IN CANCER PATIENTS: A COMPREHENSIVE APPROACH BEFORE, DURING AND AFTER TREATMENT

Zeynep Afra AKBIYIK AZ

(DDS, PhD) Istanbul University, Faculty of Dentistry,
Department of Oral and Maxillofacial Surgery, Istanbul, Türkiye
E-mail: zaakbiyikaz@istanbul.edu.tr
ORCID: 0000-0003-3606-0710

1. Introduction

Cancer is recognized as the second most prevalent cause of mortality on a global scale. (1) Based on the available data, it is projected that there will be a rise in cancer-related mortality in the forthcoming years. The primary factors contributing to this upward trend encompass the demographic shift towards an aging population, the escalation of environmental pollutants, and the growing influence of biological factors on bodily functions. (2) The global distribution of the burden of cancer is not homogeneous. While there is a rising trend in the number of new cases in underdeveloped nations, there is a corresponding decline in the number of cases observed in developed countries. In contrast, there is an observed rise in cancer-related mortality rates in underdeveloped nations when compared to their developed counterparts. The origins of these inequalities are complex and not yet fully understood. However, several factors contribute to this situation, including awareness of risk factors, dietary patterns, tobacco and alcohol consumption, overall lifestyle choices, and access to and quality of healthcare services. The identification of numerous environmental and lifestyle factors contributing to cancer risk has been established over an extended period. Notably, the utilization of tobacco and betel nut, exposure to ultraviolet light, alcohol, elevated body mass, air pollution, Human Papillomavirus (HPV) infection, and suboptimal dietary patterns have

long been linked to an increased susceptibility to malignancies. Recently, attention has turned towards the potential significance of the microbiome, particularly in relation to its role in metabolizing carcinogens. (3) Collectively, research conducted by Islami et al. suggests that, among individuals aged 30 or older in the United States, 42% of identified cancer cases and 45% of deaths attributed to cancer are linked to factors that can be modified. (4) Various cancer treatment modalities, encompassing surgical interventions, chemotherapy (CT), and radiotherapy (RT), have demonstrated significant strides in elevating patient survival rates and extending the continuum of disease management. This advancement signifies a potential amplification in the adverse consequences associated with these therapeutic modalities. While the general populace is cognizant of the typical adverse effects linked to cancer treatment, such as nausea and alopecia, there is a tendency to overlook the substantial prevalence of oral complications among individuals undergoing cancer treatment. These complications present challenges in essential activities such as food consumption, verbal communication, and swallowing. The potential ramifications of these challenges extend to impeding the efficacy of cancer treatment and diminishing overall quality of life. The oral cavity, serving as the focal point for the seventh most prevalent tumor in men and the eleventh most prevalent in women, emerges as a highly vulnerable anatomical site. The impact is particularly pronounced in the female demographic. Additionally, the oral cavity serves as the locus for the manifestation of various deleterious effects stemming from systemic cancer treatments and radiation therapy for head and neck cancer. These complications may manifest either acutely or persistently in the buccal mucosa,the maxillary bones and salivary glands. (5, 6) The administration of head and neck radiotherapy and chemotherapy can give rise to a spectrum of oral complications, spanning from xerostomia to potentially fatal infections. These issues may arise during the course of treatment or persist for an extended period of time, including months or even years following treatment. In certain cases, these complications can impose a limit on the dosage and impede, or potentially cease, the progress of cancer treatment. The prevention and management of oral complications play a crucial role in promoting effective cancer therapy, thereby improving patient survival rates and enhancing their overall quality of life.

2. Oral Complications with Cancer Therapies

The implementation of aggressive therapies for malignancies inevitably leads to adverse effects on healthy cells. Notably, the mucosal lining of the

gastrointestinal tract, including the oral mucosa, emerges as a principal focus for treatment-induced toxicity owing to its rapid turnover of cells. The oral cavity is notably susceptible to the direct and indirect toxic repercussions stemming from both cancer chemotherapy and exposure to ionizing radiation. (7) This risk arises from a combination of factors, which encompass the rapid turnover of cells in the lining mucosa, the presence of a diverse and intricate microflora, and the occurrence of oral tissue trauma during regular oral activities. The prevalent oral complications associated with cancer therapies encompass mucositis, infection, taste dysfunction, salivary gland dysfunction and pain. These complications carry the potential to precipitate additional issues such as dehydration, malnutrition and dysgeusia. Systemic infection can also originate from the oral cavity in cancer patients experiencing myelosuppression.

2.1. Radiotherapy

Radiation therapy is a highly effective treatment used to manage head and neck malignancies. Oral complications resulting from radiotherapy to the head and neck (HN) are frequently observed and extensively documented. Aside from achieving the desired treatment effects, administering high doses of ionizing radiation in the HN area leads to various undesirable but unavoidable consequences that become apparent during and after the completion of radiation therapy and may continue for the patient's entire life. Radiotherapy has an impact on various parts of the body, including the skin, bone, dentition, oral mucosa, the entire orofacial muscular complex and salivary glands. The approximate occurrence rate of oral complications during radiation therapy is approximately 40%. (8-10) Exposure to radiation in the HN region has the potential to cause permanent damage to various structures such as the oral mucosa, vasculature, muscle, and bone. It can lead to the development of mucosal atrophy and fibrosis in the salivary glands. The primary issues encountered are radiation mucositis and xerostomia. This can lead to the development of extensive dental caries, osteonecrosis, soft tissue necrosis, and trismus. (11) Regarding the time after radiation therapy, initial effects can be observed either during or immediately after RT and may persist for a period of 2-3 weeks after the completion of treatment. Acute complications can be listed as oral mucositis, infection, taste disturbance, and salivary gland dysfunction (xerostomia, sialadenitis). Acute problems commonly alleviate with time, suitable medication and guided by professional intervention. In circumstances where patients experience considerable pain during radiotherapy (RT), it becomes imperative to consider modifications to

the treatment regimen, and in certain instances, the cessation of RT may be warranted. Delayed side effects, including compromised trismus (resulting from muscle fibrosis), salivary gland functions, osteoradionecrosis, and substantial dental deterioration due to radiation caries, manifest progressively over an extended period, typically spanning months or years after the conclusion of RT. In comparison to chemotherapy, radiation-induced harm demonstrates anatomical site specificity, wherein toxicity is limited to the volumes of tissue that have been irradiated. The magnitude of harm is dependent on various factors associated with the treatment protocol, including the specific type of radiation used, the total dose administered, and the size and frequency of treatment fields. In contrast to the alterations caused by chemotherapy, radiation-induced damage is characterized by long-lasting consequences that expose the patient to continued risks of oral sequelae.

2.2. Chemotherapy

Chemotherapeutic drugs exert their anti-tumor effects by impeding the division of tumor cells, ultimately inducing their demise. However, these drugs also impact the rapidly proliferating mucosal cells and other bodily cells, resulting in the manifestation of inflammation and diverse side effects. If the side effects linked to chemotherapy agents cannot be mitigated or adequately managed, the administration of treatment may be delayed, potentially resulting in a decline in the individual's quality of life. Chemotherapy diminishes the regenerative capacity of the basal epithelium, leading to muscle atrophy, the occurrence of localized or widespread mucosal ulceration, and the induction of inflammatory responses. (12) Oral complications can occur due to risk factors that arise from both the direct harm caused to oral tissues as a result of chemotherapy and the indirect damage caused by regional or systemic toxicity. The extent of oral complications resulting from chemotherapy is contingent upon the particular treatment modality employed for each patient. The emergence of oral complications can be influenced by a range of factors, encompassing the patient's age, gender, oral hygiene practices, pre-existing oral and dental conditions, malnutrition, and low body mass index. The occurrence and intensity of these oral complications are closely connected to the degree and characteristics of systemic compromise. Commonly observed adverse effects closely associated with the administration of chemotherapeutic drugs include oral ulceration, dysphagia, odynophagia, diarrhea, nausea, vomiting, malabsorption, anorexia,

and cachexia. Around 40% of patients who undergo chemotherapy encounter the occurrence of ulcerative oral mucositis. Approximately half of these cases exhibit lesions that escalate to a level requiring medical intervention, potentially involving modifications to their cytotoxic cancer treatment. The conventional estimation for the turnover rate of oral mucosal epithelium is typically reported to occur approximately every 9 to 16 days. Intensive chemotherapy regimens have the propensity to instigate ulcerative mucositis, with discernible manifestations typically surfacing approximately two weeks following the commencement of high-dose chemotherapy. (7, 13) The dosage of chemotherapeutic drugs, as well as the application of RT, including the area treated, treatment schedule, and concurrent administration with chemotherapy, can also contribute to the development of oral mucositis. Stomatitis's consequential impacts, such as diminished oral intake and ensuing protein deprivation, exacerbate the intensity of oral mucositis by compromising the patients' restorative capabilities. The utilization of a multidisciplinary approach is imperative for the comprehensive management of oral health in individuals diagnosed with cancer, both prior to, during, and after cancer treatment.

3. Oral and Dental Management

3.1. Before Cancer Therapy

Elevated incidence and severity of oral complications in cancer patients have been correlated with poor oral health. Consequently, a aggressive approach toward stabilizing oral care is advocated prior to the commencement of treatment. A universally acknowledged pre-cancer therapy dental protocol remains elusive due to a lack of consensus within the health community. Nevertheless, it is crucial to note that essential pre-treatment interventions encompass primary preventive measures, including the adoption of suitable nutritional intake, the implementation of effective oral hygiene practices, and the timely identification of oral lesions. The time period between the detection of cancer and the commencement of therapeutic interventions is significantly short. Nonetheless, it is imperative to conduct a thorough examination of the patient's oral and dental health during this critical period, and any necessary interventions or treatments should be promptly administered. (7) The dental examination provides the dentist with the opportunity to assess the condition of the oral cavity before commencing cancer treatment, enabling the implementation of appropriate interventions that can mitigate oral complications during and after the therapy.

Ideally, it is advisable to schedule this examination at least one month prior to the commencement of cancer therapy to ensure adequate recovery time following any required invasive oral procedures.

Prior to the initiation of cancer therapy, a comprehensive oral examination guided by panoramic X-rays is recommended to assess the patient's oral health. During this phase, it is crucial to identify symptomatic and active areas of infection, particularly teeth with a low likelihood of successful treatment and non-acute pathologies that could have adverse effects on the patient's health during and after cancer treatment if not addressed. This proactive approach facilitates the early identification of potential complications during the treatment process, enabling more effective planning of treatment strategies.

During this stage, the determination of dental treatment (whether it should be radical or conservative) is contingent upon the dental and medical condition of the patient. Factors taken into consideration include the diagnosis of cancer, the treatment methods employed for cancer, the effectiveness of previous oral hygiene practices, and the amount of time available before commencing therapy. The recommended treatment plan should encompass several key components: 1) professional dental cleaning procedure (dental plaque and calculus); 2) fluoride treatment (individuals prone to dental caries); 3) elimination of infection sources; 4) elimination of sources of irritation/ mucosal trauma (sharp edges of teeth, dental restorations, or prostheses); and 5) guidance in preventive dental care. (14) It is paramount to underscore that dental treatment plans must be formulated pragmatically, considering the type and extent of dental disease, as well as the timeline until the resumption of routine dental care. Conservative treatment should not serve as a justification for postponing the onset of cancer therapy. For instance, it may be unnecessary to perform restorative procedures on teeth with minor cavities prior to initiating cancer treatment, particularly if alternative disease stabilization strategies that are less invasive, such as aggressive topical fluoride protocols, temporary restorations, or dental crowns, can be employed.

Proactive dental interventions should be undertaken before the commencement of cancer therapy, addressing prevalent caries and periodontal disease, and extracting teeth with an unfavorable prognosis, whether attributed to extensive decay and potential complications with restorative treatment. Before the initiation of cancer treatment, attention should be directed towards addressing potential sources of oral focal infection and areas prone to trauma. Such areas encompass those: areas where the periodontal pocket is >5 mm, molar teeth with furcation involvement, areas with swelling, pain, tenderness and

erythema, teeth with sensitivity to percussion, teeth with deep caries, unerupted or ongoing retained twenty-year-olds. teeth, teeth with sub-supragingival tartar, broken teeth, fillings or crowns, orthodontic bands, removable dentures used, fillings with poor edge compatibility, and fixed dentures. (15) It is imperative to eliminate these potential focal infection foci before embarking on cancer treatment. Evaluation of wisdom teeth, their eruption status, and occlusion is crucial, and decisions should be made to extract partially retained teeth, given their potential as infection foci. Remaining roots may pose a risk of infection and should be appropriately addressed. When extractions are required, timely curettage of the remaining alveolar bed and for rapid healing, it is recommended to close the tissue with primary wound closure with sutures. Ideally, these procedures should be executed at least 3 weeks before the initiation of radiotherapy for symptomatic retained teeth. For uncomplicated extractions within the irradiated area, the recommended timing is between 10 and 14 days before the commencement of radiotherapy. In cases where the tooth to be extracted is situated outside the region affected by RT, a shorter timeframe may be appropriate. (16, 17) Conditions that might cause trauma to soft tissues in prosthetics should be rectified, and if necessary, prosthetics should be renewed. Furthermore, an assessment of occlusal trauma is recommended, with the elimination of factors that may contribute to it.

The utilization of chlorhexidine solutions and dental gels prior to commencing therapy has a substantial impact on the outcomes of treatment. These substances especially contribute to the treatment of gingival diseases. Although chlorhexidine does not mitigate the severity of mucositis, it plays a crucial role in reducing the incidence of oral complications by diminishing the populations of oral mutans, streptococci, and lactobacilli. Fluoride application serves as an effective measure in caries reduction, demonstrating its highest protective impact when uniformly applied to all tooth surfaces. Monthly fluoride application is recommended for a duration of 12 months following the initiation of treatment, with potential extensions based on ongoing developments and treatment responses. (16, 18)

3.2. During Cancer Therapy

Dental and periodontal evaluations should continue during cancer treatment. Maintaining proper oral hygiene is of utmost significance for individuals undergoing chemotherapy and radiotherapy treatments. The implementation of

regular and systematic oral hygiene practices plays a crucial role in mitigating the occurrence and intensity of oral complications resulting from cancer treatment. Patients may encounter challenges in maintaining proper hygiene practices as a result of heightened sensitivity in the oral region. The utilization of less irritating components may be deemed necessary. Simultaneously, the use of mouthwashes containing chlorhexidine may offer benefits; nevertheless, in cases where such usage is not well received, alternatives such as rinsing with saturated bicarbonate solutions can be considered. (19) The maintenance of optimal oral hygiene, utilization of fluoride mouthwashes and gels, adherence to dietary regulations, and implementation of cavity prevention strategies are crucial aspects to consider during cancer treatment. To prevent demineralization and caries in teeth during radiotherapy, 1.1% sodium fluoride gel should be applied by the patient with personal dental appliances for at least five minutes every day. Routine dental care, involving gentle teeth cleaning with a soft-bristled toothbrush twice a day, coupled with mouth rinses using bicarbonate water 3-4 times a day, is advisable. Due to the occurrence of hyposalivation and xerostomia during cancer treatment, patients are recommended to take measures to alleviate the sensation of dryness. These measures may include increasing water intake, employing humidifiers to mitigate dryness, or using saliva stimulants and saliva substitutes. (20, 21) Fluoride application should commence from the first day of radiotherapy and persist as long as the saliva flow rate remains low. It has been observed that intensive oral care in patients does not elevate the risk of septicemia or oral cavity infections due to brushing, thereby reducing the likelihood of developing oral mucositis. Patients undergoing chemotherapy may experience myelosuppression, a condition characterized by a decrease in bone marrow activity, typically occurring within 1-2 weeks following chemotherapy administration. To mitigate the potential risks associated with myelosuppression, it is advisable to conduct routine oral care for these patients ideally one week prior to the scheduled chemotherapy session. Typically, if the patient does not exhibit neutropenia or thrombocytopenia, there is no inherent risk associated with administering treatment alongside consultation. It is recommended to refrain from non-essential dental procedures in the event of immunosuppression. The hematological parameters of individuals undergoing chemotherapy will exhibit a decline within a time frame of 5-7 days after the initiation of the cancer treatment regimen. However, these values will gradually revert back to their baseline levels within a span of two weeks. (15) The inter-cycle periods of chemotherapy present a favorable window for the completion of essential

oral and dental procedures. Furthermore, it is important to note that the entry of gastric acid into the oral cavity, a common occurrence during chemotherapy-induced vomiting, leads to the demineralization of dental tissues. Consequently, it is recommended that patients be instructed to rinse their mouths with water following episodes of vomiting.

3.3. After Cancer Therapy

In patients receiving chemotherapy and radiotherapy, close follow-up is mandatory after treatment and oral hygiene is very important. A comprehensive examination is mandatory to identify signs of recurrence or new primary malignant lesions, especially in cases of head and neck cancers. Preventive treatment methodologies employed before radiotherapy and chemotherapy should continue during this period. Patients experiencing hyposalivation are at a heightened risk of developing oral pathologies; hence, education and motivation should underscore the maintenance of robust oral hygiene practices and adherence to a noncariogenic diet. It is recommended that patients brush their teeth 2-3 times daily, steer clear of cariogenic foods, and undergo dental check-ups every six months. In addition, it has been observed that the application of chlorhexidine mouthwash for a period of one week every month is effective in decreasing the prevalence of Streptococcus mutans. (22, 23) The oral hygiene of individuals undergoing radiotherapy is adversely impacted by a reduction in saliva production and an increase in its viscosity. The utilization of artificial saliva has the potential to mitigate these adverse effects. The application of topical fluoride gel can be utilized as a preventive measure against the occurrence of dental caries. In order to mitigate the occurrence of osteoradionecrosis within the initial months following treatment, it is recommended that patients experiencing recurrent infections of pulpitis opt for endodontic procedures rather than extractions, even in cases where the tooth is deemed non-restorable. The incidence of medication-related osteonecrosis of the jaw (MRONJ) and osteoradionecrosis (ORN) and varies between 5% and 30%, with a notable reduction attributed to the application of intensity-modulated radiotherapy (IMRT). Given the substantial risk of ORN associated with tooth extraction following radiotherapy, it is imperative to address any potential odontogenic pathologies prior to initiating radiotherapy. (24) It is advised to refrain from undergoing dental extractions for a minimum duration of six months subsequent to receiving radiotherapy treatment. During this period, dental issues are ideally

managed through conservative treatments. However, if conservative measures prove unsuccessful and tooth extraction becomes necessary, the procedure should be performed with utmost care to minimize tissue damage. Ensuring primary closure of the wound through suturing to minimize the risk of ORN, and prophylactic antibiotics are recommended before and after the surgical procedure to mitigate the risk of complications. It is recommended to evaluate the feasibility of endodontics and coronectomy for non-restorable symptomatic teeth in patients receiving treatment with zoledronate or antiangiogenic agents. (25) Nevertheless, it is generally not recommended to perform dentoalveolar surgery on individuals who have been administered these medications at oncological dosages. If such surgery becomes necessary, preventive therapies should be employed to mitigate potential complications.

The potential risks associated with the placement of dental implants in these patients are multifactorial in nature and should be thoroughly assessed by the oncological team and dental team. (26) Determining the optimal timing for implantation in a comprehensive manner remains challenging, and the utilization of hyperbaric oxygen therapy does not appear to enhance overall survival rates. (27) According to a recent review study, implant-based rehabilitation in patients who have undergone irradiation for cancer in the HN region has been identified as an effective treatment method, demonstrating favorable survival rates despite various risk factors. (28) Nevertheless, it is imperative to conduct a thorough assessment of these risk factors in conjunction with the oncologist, considering the individual circumstances of each patient. Subsequently, treatment strategies should be customized accordingly. The review study emphasizes that the survival rates of patients with implants are significantly lower in a statistical sense when compared to patients who have not undergone irradiation. Furthermore, it has been observed that implant survival rates decrease when radiation doses exceed 50 Gy. To optimize outcomes, the implant placement should be delayed for at least six months after completing RT. Notably, in the mandible, implant usage is linked to significantly higher survival rates when compared to the maxilla region. These findings emphasize the significance of careful consideration of risk factors and personalized treatment planning in implant-based rehabilitation for individuals with a history of HN irradiation. The risk of MRONJ is elevated in patients who have undergone treatment with antiresorptive or antiangiogenic medications. Consequently, it is advisable to assess each case individually, in collaboration with the medical oncologist, prior to implant placement.

The manifestation of trismus is influenced by various factors, with surgical intervention and subsequent radiation therapy being particularly significant. Minimizing the doses of radiation therapy administered to the temporomandibular joint and the masticatory muscles is of utmost importance in order to mitigate the potential risk of trismus. The assessment of trismus requires the utilization of objective measurements to determine the extent of interincisal opening. Mouth opening can be enhanced through consistent jaw exercises and the use of dynamic bite-opener appliances. (29) Severe trismus can adversely impact oral hygiene, chewing, and swallowing functions, increasing the risk of aspiration. Patients who adhere to regular mouth opening and closing exercises recommended before the start of treatment tend to experience less impact. However, with the application of IMRT technology, a general decrease in the frequency of these exercises is anticipated. (30)

4. Conclusion

The oral health of cancer patients significantly impacts their overall quality of life. Prior to treatment initiation, a systematic dental review is imperative for patients, as oral health conditions may impact treatment efficacy and patient quality of life. During cancer treatment, minimal dental interventions are advised, prioritizing emergency treatments and preferring pharmacological approaches. Subsequent to treatment, patient rehabilitation should be evaluated, taking into account the received treatments and potential post-treatment effects. Patients receiving treatment for other neoplasms typically do not face limitations on the type of dental intervention, except for those who have been administered bisphosphonates.

In conclusion, this chapter underscores the importance of mitigating the risk of oral complications arising from cancer treatment through proactive dental evaluation and oral care before, during, and after treatment. Regular check-ups during and after treatment contribute to reducing post-treatment problems. The collaboration between oncologists and dentists is pivotal in ensuring optimal oral health outcomes for these patients.

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CHAPTER VII

DRUG INDUCED GINGIVAL OVERGROWTH

Buse Başak FEYİZOĞLU

DDS, PhD
E-mail: busebasakyilmaz@gmail.com
ORCID: 0000-0001-5276-2486

1. Introduction

Drug-induced gingival overgrowth (DIGO), also referred as drug-associated gingival enlargement, is a well-recognized undesirable effect of certain systemic drugs given for non-dental therapy where the gingival tissue is not the intended target organ.(1) It is a multifactorial condition and primarily depends on the drug's capability to induce gingival changes and the level of oral hygiene maintained by the individual. Aside from cosmetic consequences, patients with DIGO may encounter significant discomfort, challenges in speech and chewing, pain, and tooth loss.(2,3)

The term "gingival enlargement" or "gingival overgrowth" has replaced "gingival hyperplasia" (increase in cell number) and "gingival hypertrophy" (increase in cell size) as they are histological diagnoses that do not accurately describe the pathological processes present within the tissues.(4,5) It is well established that real gingival enlargement requires alterations in cell size, cell proliferation, gingival vasculature, and the extracellular matrix.(6)

DIGO is primarily associated with three types of drugs: anticonvulsants, immunosuppressants, and calcium channel blockers (CCB).(4) The first large case series of DIGO was reported in 1939, revealing DIGO in 68 out of 119 patients who were undergoing treatment with the antiepileptic drug phenytoin. (7) Since then, more than 20 different drugs have been reported to be associated with gingival overgrowth.(2,5) Bondon-Guitton et al. reported that gingival overgrowth is not exclusively associated with CCBs, cyclosporine, and

phenytoin; it can also occur with other immunosuppressants, anticonvulsants, antibiotics, and oral contraceptives.(8)

DIGO has a complex pathophysiology because of a multitude of interacting factors that are postulated to be involved. Drugs have an antagonistic impact on sodium and calcium channels, thus decreasing intracellular Ca2+. This results in reduced intracellular levels of folic acid due to reductions in folic acid (FA) uptake. These events lead to disturbed cellular function such as dysregulation of collagenase activity that induces gingival enlargement.(9,10)

2. Types of Drugs

2.1. Anticonvulsants

Phenytoin is the most frequently prescribed anticonvulsant agent for the treatment of epilepsy, especially for grand mal, temporal lobe, and psychomotor seizures. The first cases of gingival overgrowth as a result of phenytoin usage were reported soon after it was introduced.(11,12) Phenytoin-Induced Gingival Overgrowth is particularly an issue observed in older children and young adults, being exceptionally rare in individuals who are edentulous.(12) Gingival overgrowth can manifest within three months of initiating the dosage and tends to progress most rapidly during the first year of using the drug.(13) The gingival growth typically initiates as a diffuse swelling of the interdental papillae, which enlarges and merges, resulting in a nodular appearance.(11) It mostly occurs in the vestibular region of maxillary and mandibular anterior teeth. There are studies reporting a positive relationship between the severity of gingival overgrowth and plasma phenytoin level.(13,14)

Cases of gingival enlargement following the chronic use of carbamazepine, phenobarbitone or valproic acid in adult patients have been reported, but such instances are rare or have been inadequately documented.(4)

2.2. Calcium Channel Blockers (CCB)

CCBs are drugs that are prescribed for the treatment of hypertension, angina pectoris and cardiac arrhythmias. Hypertension stands as the primary preventable risk factor for cardiovascular disease (CVD) and all-cause mortality globally. The prevalence of hypertension is increasing, attributed to the aging population and heightened exposure to lifestyle risk factors, such as unhealthy diets and insufficient physical activity.(15) It is anticipated that the number of adults with hypertension will rise by approximately 60% by 2025, reaching a total of 1.56 billion people with the condition.(16)

The demand for antihypertensive drugs is on the rise globally. As more individuals are prescribed antihypertensive drugs, there is a potential increase in adverse effects, such as gingival overgrowth.(17) Gingival overgrowth is a common occurrence in the treatment with dihydropyridines, characterized by the accumulation of extracellular matrix (ECM) within the connective tissue of the gingiva. It typically manifests within the first month of the treatment.(18) Nifedipine is a dihydropyridine group calcium channel-blocking agent extensively utilized as a vasodilator for the treatment of hypertension and ischemic heart disease. It is one of the CCBs that has been associated with gingival overgrowth. The prevalence varies between 30% and 50% in Nifedipine-treated patients, compared to a prevalence of 5% in untreated controls.(19)

Other CCBs that are associated with gingival overgrowth include amlodipine, nitrendipine, felodipine, cilnidipine, manidipine, nisoldipine, nicardipine, diltiazem and verapamil.(17) Amlodipine is a CCB from dihydropyridine group with structural similarities to nifedipine. Amlodipine-induced gingival enlargement typically initiates at the interdental papilla and occurs within the first 6 months of starting drug therapy, particularly at a dose of 10 mg/day. However in a limited number of cases, gingival enlargement induced by amlodipine has been reported, even at a dose of 5 mg, when the medication is used for more than 6 months.(20,21)

Gingival overgrowth induced by CCBs primarily affects the anterior teeth rather than the posterior ones, with more pronounced effects on the facial/buccal surfaces compared to the palatal/lingual surfaces. In severe cases, the entire papillae and surrounding tissues become enlarged, resulting in a lobulated appearance of the gingival tissues. The enlargement may extend coronally, leading to interference with mastication and speech. Additionally, esthetic issues may arise if the enlargement involves the anterior teeth.(22)

2.3. Immunosuppressants

Immunosuppressive drugs, aimed at preventing the rejection of transplanted organs, have significantly improved the success rates of organ transplant surgeries.(23) Cyclosporine A, a hydrophobic fungal metabolite, is a powerful immunosuppressant commonly employed as the primary choice to counteract rejection phenomena in organ transplantation patients. It is also utilized for the treatment of various autoimmune diseases.(24) The prevalence of gingival overgrowth induced by Cyclosporine A varies from 25% and 81%, depending on the study population and the index used. It usually manifests within the first 12 months of taking the medication. Higher doses of cyclosporin

and the concomitant use of CCBs were shown to significantly increase the risk and severity of gingival enlargement. The enlargement can manifest as localized or generalized, ranging from mild to severe, and may interfere with speech, mastication, and oral hygiene practices. Generally, it tends to be more severe in the anterior and vestibuler regions of the mouth.(25–27)

Tacrolimus (formerly known as FK506) was introduced as an immunosuppressive agent for organ transplants in 1987 and has been gradually gaining popularity. Its pharmacodynamics are very similar to Cyclosporine A and it has been shown to be an excellent alternative to Cyclosporine A, leading to similar success rates in organ graft survival.(23,25,28) Paixao et al. compared the incidence and severity of gingival overgrowth induced by Tacrolimus and Cyclosporine A. it was concluded that there is either no gingival overgrowth in the Tacrolimus group or it initiates later, and tends to be less severe.(23) Greenberg et al. also confirmed that tacrolimus is not associated with gingival enlargement.(25)

3. Risk Factors

3.1. Plaque

The severity of gingival overgrowth in patients using these medications aligns closely with inadequate plaque control and corresponds with the level of inflammation induced by plaque.(4) Inflammation induced by plaque can worsen the impact of medications, resulting in a synergistic effect on the gingival tissues and causing excessive gingival enlargement.(29) In drug-influenced gingival conditions, the presence of plaque bacteria in conjunction with the drug is essential for triggering a gingival response. However, not all patients taking these drugs will develop gingival enlargements, indicating a susceptibility that may involve specific characteristics.(30,31)

The significance of plaque as a crucial cofactor has been acknowledged in the classification of periodontal diseases in 1999. In this classification, “drug-influenced gingival enlargements” are categorized under “Dental plaque-induced gingival diseases”.(32)

Numerous authors have proposed that dental plaque is a crucial element in the onset of gingival overgrowth. Nevertheless, a definitive correlation has yet to be established. Some researchers have reported that gingival overgrowth might be more pronounced in individuals with inadequate plaque control. On the contrary, other studies have indicated that conventional periodontal treatment,

coupled with a comprehensive oral hygiene regimen, can lead to a favorable response in treatment.(30,33,34)

3.2. Age

Age has been considered an important risk factor for DIGO with particular reference to phenytoin and cyclosporin. Gingival overgrowth appears to be more prevalent in children and teenagers, indicating a potential hormonal component in its susceptibility. Age is not a relevant risk factor for CCBs, as these medications are typically prescribed for individuals in the middle-aged and older adult population.(29,30)

3.3. Gender

Males are reported 3 times more likely to develop overgrowth than females in a study with patients taking nifedipine.(35) However Seymour et al. suggested that several studies on cyclosporin exhibit a notable male bias due to the higher prevalence of organ transplantation, particularly heart transplants, among men. (30) The authors also concluded that there is growing evidence showing that males are more susceptible to developing gingival overgrowth than females when it comes to both cyclosporin and CCBs, and the gingival changes tend to be more severe in males.(30)

3.4. Drug Variables

The connection between the degree and severity of gingival overgrowth and various drug-related factors, such as dosage, duration of use, and serum and salivary concentrations, remains a topic of controversy. The variability observed in the studies is often attributed to differences in the methodology used to assess gingival overgrowth, the timing of blood sample collection, the size of the patient population under investigation, and the clarification of other factors that can influence a drug's pharmacokinetic profile.(30)

3.5. Concomitant Medication

There have been reports of interactions between concurrently administered medications that impact gingival enlargement. The chronic use of phenytoin and other anticonvulsant agents in adult epileptic patients does not influence the extent of gingival enlargement.(36) On the contrary, individuals undergoing

treatment with Cyclosporine A while also taking a CCB exhibit more severe gingival lesions compared to those solely medicated with Cyclosporine A. The selection of the CCB used alongside Cyclosporine A can also impact the occurrence or intensity of gingival enlargement. Reports indicate that renal transplant recipients on Cyclosporine A and amlodipine have a higher prevalence of gingival overgrowth compared to those receiving Cyclosporine A and nifedipine.(37)

4. Treatment

4.1. Non-surgical Treatment

The approach to treating DIGO should be tailored to the specific medication in use and the unique clinical presentation of each case. The most effective treatment for DIGO involves discontinuing or substituting the medication. In that case it was reported that resolution of gingival lesions may take 1 to 8 weeks. However not all patients, particularly those with long-standing gingival lesions, may respond positively to this treatment method.(4,38)

Substitute medications for phenytoin include carbamazepine and valproic acid, both of which have been reported to have a milder impact on inducing gingival enlargement.(38) The possibility of substituting phenytoin has expanded with the introduction of a new generation of anticonvulsants, including gabapentin, lamotrigine, topiramate and sulthiame.(4)

For patients using nifedipine, with reported gingival enlargement prevalence of up to 44%, alternative CCBs like diltiazem and verapamil could be considered. The prevalence of gingival enlargement associated with these drugs is reported to be 20% and 4%, respectively. Additionally, it should be considered using a different class of antihypertensive medications other than CCBs, as none of them are known to induce gingival enlargement.(38)

Tacrolimus serves as an alternative immunosuppressant for renal transplant recipients and is notable for not being associated with gingival enlargement.(4) It has been demonstrated that gingival enlargement induced by cyclosporin can spontaneously resolve when the drug is replaced with tacrolimus.(39)

The administration of systemic antibiotics, such as a short course of azithromycin (3-5 days, 250 to 500 mg/day), may impact the remission of DIGO, with remission periods ranging from three months to two years.(40) Conde et al. reported that roxithromycin may be used as an important therapeutic tool to reduce cyclosporin-induced gingival overgrowth.(41)

The dental proffesionals should prioritize plaque control as the initial step in treating DIGO. While the precise role of bacterial plaque in DIGO remains unclear, evidence suggests that maintaining good oral hygiene and regularly removing plaque professionally can reduce the extent of gingival enlargement and enhance overall gingival health.(38,42)

4.2. Surgical Treatment

Despite efforts to substitute the drug and maintain good plaque control, DIGO may persist. In that case, periodontal surgery, either gingivectomy or the periodontal flap, should be adopted. Surgery is often carried out also for esthetic reasons, especially when the anterior labial gingiva is frequently affected by gingival enlargement.(4,38)

DIGO can be managed using various techniques. Laser excision, in particular, has been associated with a lower rate of recurrence. The technique also has some distinct advantages in cases where the patient has underlying problem with haemostasis.(43)

5. Conclusion

DIGO is a multifactorial adverse effect associated with the use of certain systemic medications. It remains a significant oral health issue and the exact pathogenic mechanisms are not yet completely understood. Cyclosporine A, phenytoin and nifedipine are the drugs which most commonly cause DIGO. Treatment generally focuses on substituting the drug and controling local inflammatory factors, such as dental plaque. Further investigations are essential to thoroughly establish the pathogenesis of gingival overgrowth and to generate novel information for future preventative and therapeutic measures.

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CHAPTER VIII

DIABETES AND PERIODONTITIS

Buse Başak FEYİZOĞLU

DDS, PhD
E-mail: busebasakyilmaz@gmail.com
ORCID: 0000-0001-5276-2486

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic condition stemming from the body's inability to either generate the hormone insulin or efficiently utilize the insulin it produces. Insulin, a hormone produced by the pancreas, facilitates the transfer of glucose from the bloodstream to cells for energy. The absence of this crucial hormone leads to the buildup of glucose in the bloodstream, potentially causing severe and life-threatening complications.(1,2) Type 2 diabetes mellitus (DM2) is the most prevalent form of diabetes, constituting 85% of all individuals with diabetes.(3) On a global scale, the estimated number of adults with diabetes mellitus (comprising both type 1 and type 2) was 285 million in 2010, and projections suggest that it will increase to 439 million by the year 2030. From 2010 to 2030, there is anticipated to be a 69% surge in the count of adults with diabetes in developing countries, while developed countries are expected to experience a 20% increase.(4)

Periodontal disease refers to a chronic inflammatory condition that leads to the destruction of the periodontal tissues. It describes a wide range of reversible and irreversible diseases and is a major public health issue.(5,6) The two most common periodontal diseases are gingivitis and periodontitis. Gingivitis is the inflammation of the gingiva which is limited to the soft-tissue compartment of the gingival epithelium and connective tissue, while perioedontitis is characterized by progressive destruction of the periodontal tissues.(7,8) Periodontitis is the most common chronic inflammatory non-communicable disease of humans according to the epidemiological studies.(9,10)

Hyperglycemia, the defining characteristic of diabetes mellitus, is linked to various complications, potentially impacting all organs in the body, including the periodontal tissues surrounding the teeth.(11) Numerous researchers have investigated the correlation between diabetes and periodontal diseases over time. Findings indicate that individuals with diabetes face a 2-3-fold elevated risk of developing severe periodontitis and experiencing periodontal disease progression.(12,13) The aim of this book chapter is to present recent ınformation on the relationship between periodontitis and diabetes, considering the latest discoveries in the field, and offer beneficial data to professionals in both fields in order for them to understand the bidirectional interconnections between these distinct pathological entities.

2. Diabetes

Diabetes is a complex metabolic disorder with several etiologic causes, characterized by persistent hyperglycemia (elevated blood glucose levels). The state of hyperglycemia typically results from reduced insulin secretion and/or diminished insulin action.(14–16) Diabetes stands as one of the rapidly expanding diseases globally, with projections estimating its impact on 693 million adults by the year 2045.(17)

Early symptoms encompass various manifestations such as polyuria (excessive urination), polydipsia (excessive thirst), polyphagia (excessive hunger), blurring vision, and weight loss. The intensity and combination of these symptoms depend on the timing of the diabetes diagnosis.(14) Hyperglycemia contributes to the development of complications associated with diabetes, resulting from the prolonged damage, dysfunction, and failure of various organs and systems; such as the eyes (retinopathy), heart (cardiovascular diseases), kidney (nephropathy), brain (cerebrovascular diseases, cognitive dysfunction, stroke), blood vessels (increased risk of the atherosclerotic process), nerves (neuropathy). These complications have a significant impact on overall well-being and quality of life.(18)

The most common forms of diabetes are type 1 diabetes and type 2 diabetes. Type 1 diabetes is characterized by the body’s incapacity to produce insulin as a result of the autoimmune destruction of beta cells in the pancreas. It is the predominant form of diabetes in children. While the onset of the disease is most commonly observed in children, it can also occur in adults.(14,19) Type 2 diabetes constitutes approximately 90% of diabetes cases and arises from a combination of impaired insulin secretion and heightened insulin resistance.

The incidence of type 2 diabetes rises with age, and most diagnoses occur after the age of 40, although there is an observed increase in its occurrence among younger adults and children. Lifestyle factors, including overweight/obesity and insufficient physical activity, are commonly associated with type 2 diabetes.(15)

The management of diabetes focuses on maintaining blood glucose levels within normal limits. Meticulous control of hyperglycemia is crucial for preventing complications associated with diabetes. The effectiveness of this control is assessed by monitoring glycated serum proteins, particularly glycated α-hemoglobin (HbA1c). Since HbA1c becomes incorporated into red blood cells, it provides an indication of average serum glucose levels over the preceding 2 to 3 months.(20)

3. Periodontitis

Periodontitis is a multifactorial chronic inflammatory disease characterized by progressive destruction of the tissues surrounding and supporting the teeth. (21) The pathogenesis of periodontitis is based upon a circular relationship between the microbial dental biofilm and the host's inflammatory immune response.(22) Bacteria are essential for the disease to start, as in gingivitis, where their removal leads to the reversal of this inflammatory condition. The microbial community profile should shift to a disease-associated level, known as dysbiosis. Last but not least, unregulated inflammatory and immune responses are also largely accountable for tissue destruction.(23,24)

One of the most characteristic features of periodontitis is the activation ofosteoclastogenesis and the destruction of alveolar bone ultimately leading to the loss of periodontal tissue support, manifested through clinical attachment loss (CAL). If not treated, it may eventually cause tooth loss, adversely affecting chewing function, aesthetics, and diminishing overall quality of life.(21,25) It is a significant factor leading to edentulism and masticatory dysfunction, also having a negative impact on general health and resulting in substantial dental care costs.(26,27)

Mild and moderate forms of periodontitis are highly prevalent among adult population, with prevalence rates around 50%.(28) The severe form of the disease tends to increase particularly between the third and fourth decades of life, with a global prevalence of approximately 10%. (29)

The primary etiology of periodontitis is the bacteriel infection, but it alone is not sufficient to initiate or progress the disease. Bacteria-derived factors and antigens stimulate a local inflammatory reaction and thus activate the innate

immune system. Mediated by toll-like receptors (TLRs) from resident cells, host cells recognize microbial components and this leads to the release of proinflammatory cytokines and recruitment of phagocytes and lymphocytes. Activation of T and B cells initiates the adaptive immunity and the producton of antibodies. These host inflammatory factors including cell populations, cytokines and other molecules, and the complex interactions among them are the main cause of the destruction of tooth supporting tissues.(7,8,30,31)

Prevention and treatment of periodontal disease start with oral hygiene procedures in order to remove the periodontal biofilm from teeth. Professional treatment includes plaque and calculus removal by scaling and root planing. The non-surgical therapy is not sufficent for patients with severe periodontitis. In that case periodontal surgery are used to reduce periodontal pocket depths and stimulate regeneration of periodontal tissues by various surgical procedures. Supportive follow-up therapy after active treatment is mandatory in any case to maintain periodontal health.(32)

4. Diabetes and Periodontitis

Periodontal disease and diabetes mellitus are both common, chronic diseases worldwide. The relationship between periodontal health and diabetes can be described as bidirectional(12,33), although periodontitis is also referred as the sixth complication of dibetes.(34)

Both diabetes and periodontitis are associated with enhanced inflammation and impaired immunological responses. Systemic inflammatory cytokines, such as interleukin-1beta and interleukin-6, and the acute-phase inflammatory marker, C-reactive protein, are elevated in Type 2 diabetes as well as in periodontitis.

There are several studies examining the effect of periodontal treatment on diabetes outcomes. Emerging evidence shows that periodontal therapy may have a positive effect on glycemic control in diabetic patients. A meta-analysis by Artese et al. concluded that periodontal therapy reduces systemic inflammation in Type 2 diabetes patients.(35) Another meta-analysis reported that periodontal treatment leads to improvement of the general health of type 2 diabetic patients by positively affecting the metabolic control as in improvement of glycemic control for at least 3 months.(36) Baeza et al. also concluded that periodontal therapy has an impact on metabolic control and reduction of systemic inflammation of patients with Type 2 diabetes.(37) According to a review by Borgnakke et al., current evidence indicates that periodontal disease may have an adverse impact

on glycemic control, contribute to diabetes complications, or potentially play a role in the development of type 2 diabetes.(38) Another meta-analysis by Engebretson et al. reported that following periodontal therapy in patients with type 2 diabetes, modest reduction in HbA1c was observed across studies which is consistent with several systematic reviews.(39) Wang et al. demonstrated that periodontal treatment results in a reduction of HbA1c in diabetic patients with periodontitis, particularly within the first three months post-treatment. However, it was noted by the authors that the improvement in periodontal status may not exhibit a noticeable effect on glycemic control for diabetic patients within the six months following treatment.(40) Although there are many randomized trials reporting a better glycemic status of type 2 diabetes patients after periodontal treatment(41,42), Engebretson et al. concluded that non-surgical periodontal therapy did not result in an improvement in glycemic control for patients with diabetes and moderate to advanced chronic periodontitis.(43)

Multiple studies have verified that individuals diagnosed with diabetes exhibit a higher prevalence of periodontal diseases when compared to those who are healthy.(44) Kaur et al. established an association between both Type 1 and Type 2 diabetes and an elevated severity of periodontal disease and tooth loss when compared with non-diabetic subjects in a large and homogeneous study population.(45)

Periodontitis can negatively impact glycemic control in individuals with diabetes mellitus and contribute to the development of complications associated with diabetes. The detrimental impact of periodontal infections on diabetes mellitus may be attributed to the subsequent rise in systemic inflammation, a factor that contributes to insulin resistance.(11)

5. Conclusion

There is supporting evidence showing the bidirectional relationship between diabetes and periodontitis. Diabetes is linked to an increased occurrence and progression of periodontitis, and, conversely, periodontal infection is associated with poorer glycemic control in individuals with diabetes. There is a crucial need for increased patient awareness regarding the interconnection between diabetes and periodontal diseases. It is imperative to establish a co-management model of care that involves collaboration between medical and dental professionals for individuals affected by both conditions. Further research is essential to establish the best prevention and treatment modalitites.

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CHAPTER IX

THORACIC DISC HERNIATION

Abdullah Talha ŞİMŞEK

Istanbul Medeniyet University
Faculty of Medicin, Department of Neurosurgery,
E mail: simsektalha@hotmail.com
ORCID: 0000-0002-8668-3935

1. Introduction

Thoracic disc herniation is a rare condition that usually presents with back and abdominal pain and myelopathy and loss of sphincter function in advanced stages without specific complaints. With Magnetic Resonance, the level of disc herniation and the location of the disc herniation can be easily seen. Currently, different surgical methods have been developed depending on the localisation of the disc herniation. These methods have various advantages and disadvantages according to the localisation of the disc herniation. The surgeon decides on the surgical approach according to the level and position of the disc herniation. Thoracic disc herniation and surgical approaches are described in this section.

2. History

Thoracic disc herniation was first described by Key in 1838.In 1911, Middleton and Teacher presented a paraplegic case due to thoracic disc herniation.The first thoracic disc herniation surgery was performed by Adson in 1922.In 1994, Rosenthal et al. described endoscopic thoracic disc herniation surgery.(4,12)

3. Epidemiology

Thoracic disc herniation is seen in approximately 1% of all disc herniations. (1) The intervertebral disc is the region with the least volume. And it is the

area where the ribs also articulate with the thoracic vertebrae. Movement to the cervical and lumbar region is less common.(10) It is often seen in middle age. It is higher in men with a rate of 60%. The T11-12 distance with the highest level of movement is the most commonly affected disc herniation region.(18) The prevalence of asymptomatic cases was 15%. Thoracic disc herniation, which causes neurological deficit, is seen in one in a million.(9)

4. Etiology

Thoracic vertebrae are less exposed to degeneration than the cervical and lumbar region. The articulation of the costas with the vertebrae increases stability in this area and acts as a support. However, when the load on the disc intervals is excessive, annular tears in the disc structure, hypertrophy and osteophytes begin to occur in the adjacent vertebral end plates. Patients due to degeneration present clinically with complaints of pain. Pain may be axial due to degeneration or radicular type due to disc herniation.(6) Compression of the spinal canal at the thoracic level can be caused by hypertrophy of the ligamentum flavum, hypertrophy of the facets, osteophytes and ossification of the posterior longitudinal ligaments. Thoracic disc herniation due to trauma can be mostly caused by torsion and bending. (6)

5. Clinical

Patients may present with back, lumbar and leg pain. Myelopathy due to spinal cord compression may present with difficulty in walking, instability and imbalance due to upper neuron damage. Abdominal and cramsteric reflexes should be taken into consideration during the examination and clonus and babinski reflex can be seen. In the root compressions that occur depending on the level of the disc herniation, pain and numbness occur in the form of a generation that shows the level. Horner's syndrome can be seen in disc herniations at T2-T5 levels. Patients may present with droopy eyelid, pupillary construction, dry eye and pain radiating down the arm.(13,25)

6. Differential Diagnosis

Back pain, which is the most common complaint seen in thoracic disc herniation, can also be seen in other pathologies. Patients with chest pain, nonspecific pain in the abdomen or inguinal region may be confused with conditions such as cardiology, esophagitis, gastrointestinal ulcers. Therefore,

when diagnosing thoracic disc herniation, systemic examination should be considered and supported by laboratory and imaging methods. Similar symptoms can be observed in tumors of the spine. It can be distinguished by contrast-enhanced MR images (ependymoma, astrocytoma, meningioma, etc.). Spinal metastases are most commonly seen in the thoracic region.In suspicious cases, PET and scintigraphy should be performed in addition to MR and CT imaging. In cases of spinal infection, hemogram and acute phase reactants should be seen in addition to contrast-enhanced MRI. Similar clinical conditions due to compression occur in spinal arteriovenous malformations. Spinal DSA methods should also be applied. In neurodegenerative diseases such as Multiple Sclerosis and transverse myelitis, CSF findings are also valuable in addition to MRI. Chronic back pain is seen in rheumatological diseases such as ankylosing spondylitis and fibromyalgia. In these cases, laboratory findings are important.(2,3)

7. Prognosis

Prognostically, 77% of patients with radiculopathy due to thoracic disc herniations improved with conservative treatment, while the radiological size of the disc herniation was also found to be a factor in the shrinkage of the disc over time.Disc hernias with 10% or less channel invasion were observed to shrink over time, while disc herniations with 20% or more canal invasion did not shrink over time. (24,6)

8. Diagnosis

Neurological examination as well as radiological imaging are the gold standard in the diagnosis of thoracic disc herniations. Osteophytes, narrowing of the disc gap and facet hypertrophies can be seen in the aged, degenerated intervertebral disc area with direct radiographs. CT myelography is used in patients who cannot undergo MRI. CT better shows calcified discs, ligaments and facet joint degenerations. In this way, it is understood that the symptoms are more severe in calcified discs.(Image 3,4) MRI is the best method for showing soft tissues.(Image 1,2) It is more effective in terms of showing annular defects in the disc structure, the condition of the anterior, posterior ligaments, anatomical formations such as the structure of the facet capsule. Thoracic disc herniation is most commonly seen between T11-L1 distances. This region is the thoracolumbar transition region. (8,6)

9. Medical Treatment

Medical treatment can be applied in patients without significant cord compression and neurological damage in thoracic disc herniation.First, NSAIDs are started. If radiculopathy is observed, gabapentin or tricyclic antidepressants may be prescribed. In physiotherapy, a decrease in symptoms can be seen with directions such as massage. Epidural steroid and local anesthetic applications have been shown to be beneficial in patients with thoracic disc herniation and central canal stenosis. However, it is emphasized that transforaminal injections in radiculopathies are not beneficial and may cause root damage. Dorsal root ganglion and intercostal nerve radiofrequency applications are also performed.(15,17)

10. Indications for Surgical Treatment

In patients who are planned to undergo surgery in thoracic disc herniation, the objectives are divided into 3 groups;

1-If there is neural compression, providing decompression
2-Stabilization if there is instability next to neural compression
3-Correction of neural compression if there is deformative deformity next to neural compression.

Surgical methods are performed to achieve these goals. If we group it as a symptom;

1-Patients with pain and/or radiculopathy only
2-Patients with myelopathy
3-Patients with loss of strength of the lower extremities

In the group within the first item, surgery is applied in resistant patients who do not respond to medical treatment, while surgery is applied in articles 2 and 3.

11. Surgical Techniques

11.1 Transpedicular Approach

This method is used in calcified or soft lateral and paramedian disc herniations. The low amount of bone removed is a preferable method for postoperative patient pain and comfort due to the low amount of intervention.

As a surgical technique, the patient is taken to the table in the prone position. After the disc distance to be operated is determined by scopy, the skin is crossed subcutaneously with the midline vertical incision. According to the side of the disc, the paravertebral adeles are stripped subperiosteally. Lamina, facet and transverse processes are stripped so that they can be seen. In the transpedicular approach, the vertebral corpus is reached by entering the pedicle below the disc level with the help of a drill. The corpus structures adjacent to the disc are excised with the help of curette. Also the pedicle is taken up to the cord distance. The medial facet is taken from the joint. After the spinal cord is opened so that it can be seen, discectomy is performed by inizing the intervertebral disc laterally. During surgery, the lateral and inferior sides of the pedicle and facet should be protected for stabilization. In a study conducted by Bilsky, transpedicular approach was applied to 20 thoracic disc herniations and 17 of them did not develop postoperative pain and instability.3 had minor complications and no postoperative kyphosis or instability.(5)

11.2 Transfacet Approach

In this approach, the surgical position and approach are the same as the transpedicular approach. However, in this method, only partial hemilaminectomy and facet bone resection can be performed and used in lateral soft thoracic disc herniations. This approach is not appropriate in midline and calcified disc herniations. Lung complications are not seen due to the posterior approach such as transpedicular.(23)

11.3 Transforaminal Approach

This approach is preferred with factors such as the small amount of resected bone, the absence of lung complications, the short length of hospital stay, and the use of a microscope to provide a 3-dimensional image. In the surgical technique, after the patient is taken to the table in the prone position, the paraspinal adeles are dissected by digital dissection after the fascia is insected through a 2-3 cm vertical incision made 6-7 cm laterally of the midline. The facet at the disc distance determined by scopy is seen laterally to the joint. After the transverse bones and intertransverse ligament are detected, the separator is placed. At the junction of the transverse proces and the pedicle, the root and foramen appear. The root is relieved by performing a foraminotomy. Disc herniation is reached. Discectomy is performed. It is a minimally invasive effective approach in terms of patient comfort.(14,16)

11.4 Posterolateral Approaches, Costatrotransversectomy

This procedure provides wider visibility for midline calcified discs, osteophytes and lateral disc herniations. Pleural complications may occur in this procedure. Especially in T1 disc herniations, caution should be exercised during dissection. Weaknesses of the upper extremities may be observed. In other distance discs, the roots can be sacrificed during this method. In high-level discs, the scapula is tried to be excluded so that the arm is raised for scapula removal. In this procedure, after the patient is positioned in the prone, paramedian, T or half moon shaped incisions are started. Paravertebral muscles are excluded so that the rib, transverse bone and joint area is seen. Transverse proces and Costa proximal are taken.(Image 7) Foramen and disc distance are seen. Foraminotomy and discectomy are performed. In addition, thanks to the wide field of view in this method, instrumentation materials such as screws or cages can be applied when stabilization is required.(7,21)

11.5 Lateral Extracavitary Approach

This approach is a necessary method to provide a wider viewing angle in thoracic disc herniation than the methods we have mentioned so far and to reach the osteophytes or disc herniations in the central region. However, this method has additional disadvantages such as the amount of resected bone being higher, the surgical time being long, and the blood loss being higher. This method is not applied in patients whose general condition is not good and who cannot tolerate it. In this method, it provides a wider viewing angle by approaching laterally compared to costatransverseectomy. In this way, the necessary instrument applications for stabilization after discectomy can be performed in the same procedure. The patient is taken to the table in the lateral decubitus or prone position. In disc hernias above T6 level, it is necessary to exclude the scapula. As an incision, the median incision line is extended adjacent to the lower edge of the scapula. An incision is made in the form of a hockey stick. In disc herniations below T6 level, the same incision is made as the costatransversectomy incision. After the incision, the trapezius and rhomboid muscles are excluded laterally, the rector spina and transversospinalis muscles are excluded medially. By paying attention to the costal intercostal nerves at and below the disc level detected by scopy, 9-10 cm from the posterior part is resected. Then, the retropleural fault and pleura are pushed anterolaterally to reach the surgical area. Central discs and osteophytes can be reached by this method. Discectomy and vertebral corpus can be resected. If necessary, cage grafts can be placed.(11,26)

11.6 Transthoracic Approaches

With this method, the distance of thoracic disc herniation from the anterior is reached, it is used in central or paracentral disc herniations and osteophytes of this region. It is also a preferred method in multi-level disk herniations. Since the transthoracic approach is an approach in which neurosurgeons have little experience, it is less preferred than other methods. Surgeries performed together with a thoracic surgeon are safer. In this method, an increase in postoperative patient pain is observed. The surgical position is performed in the full side supine position by entering between the 2 upper elevations of the level. After the latissimus dorsi muscle is dissected, the jeans are revealed with the help of cautery by paying attention to the vascular nerve packages. It is entered between the elevations with the help of an etractor. In general, the patient is given a position with the left side on top. That side is extinguished with the help of a lung tube. The parietal pleura is insected to reach the distance of the vertebrae and disc. The proximal of the jeans is excised. In addition, the procedure is facilitated by performing hemicorpectomy. Cord damage is rarely seen because it is approached from the front. However, this level is a region with little blood and low spinal cord thickness. Care must be taken in terms of cord damage. Turling the peidules at the level of compression is useful in determining the boundaries of the spinal canal. In addition, resection to the upper and lower end plates provides a wider surgical corridor.(Image 5,6) (19,20)

Image 1 and 2: Sagittal T2 and Axial T2 sequences show median hypointensity, chorda compression, calcified disc herniation.

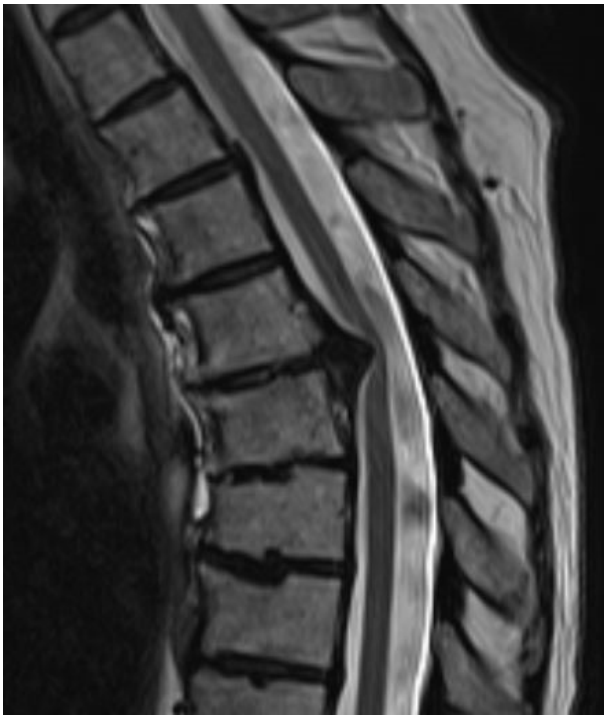

Image 1

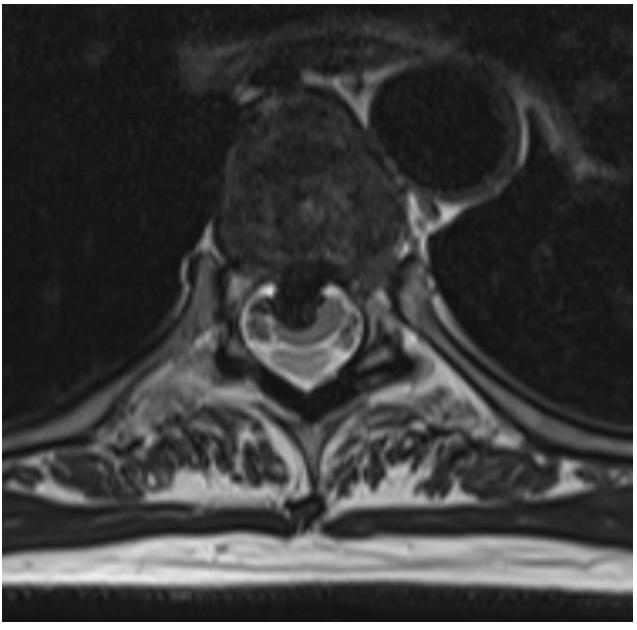

Image 2

Image 3and 4: Sagittal and Axiyel CT shows a calcified thoracic disc herniation.

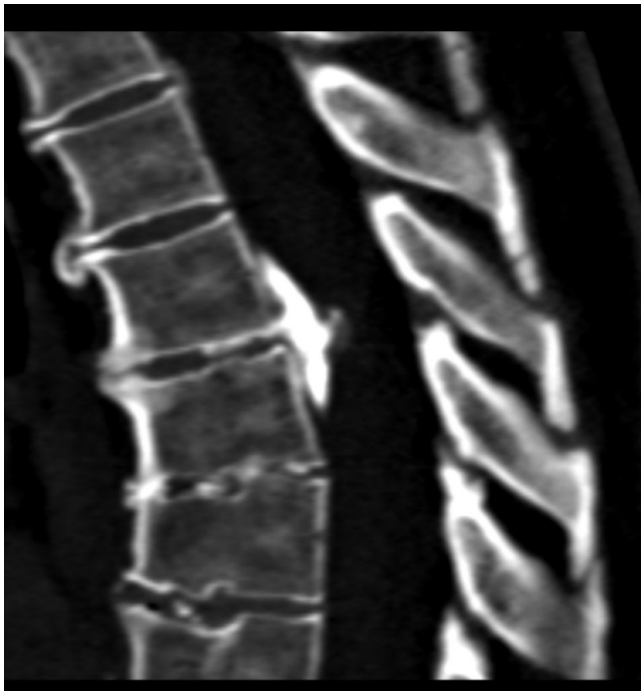

Image 3

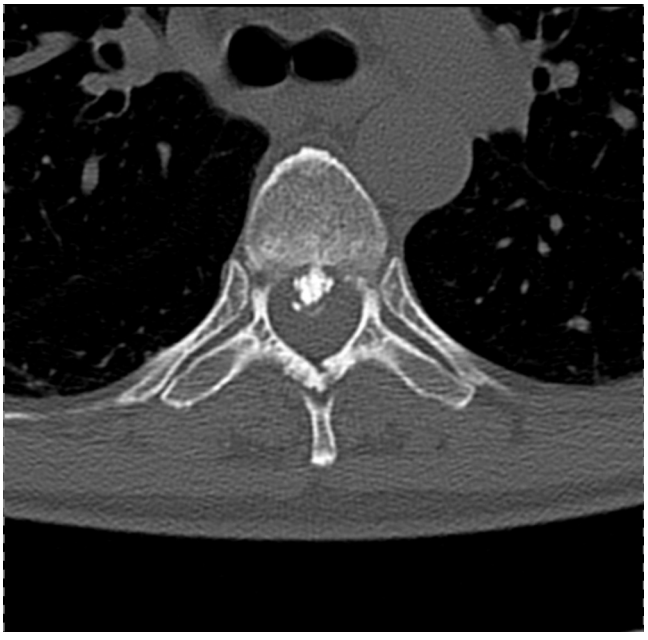

Image 4

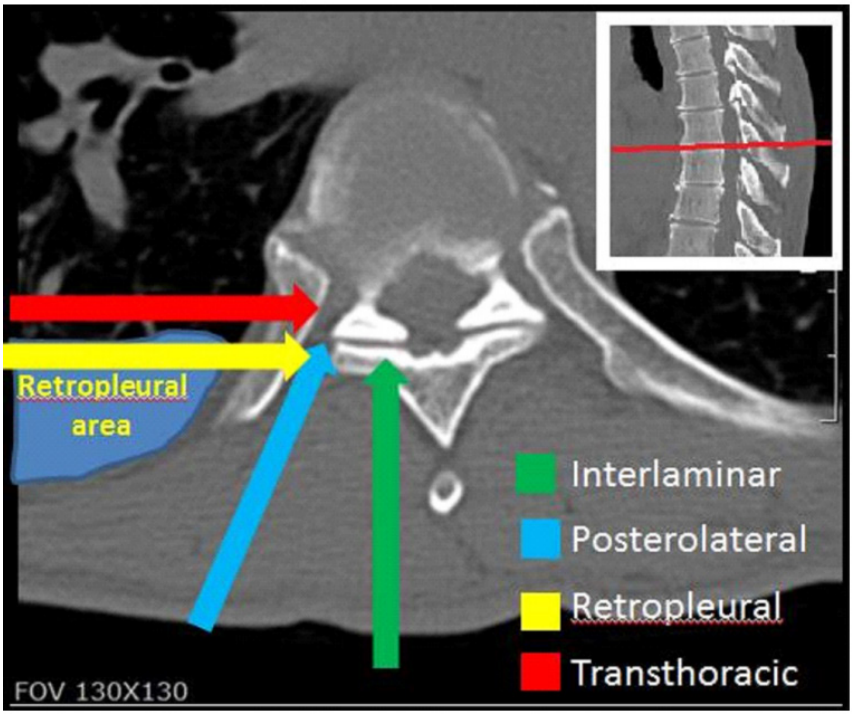

Image 5: An axial cut through the T8–9 level showing the directions of various approaches.(22)

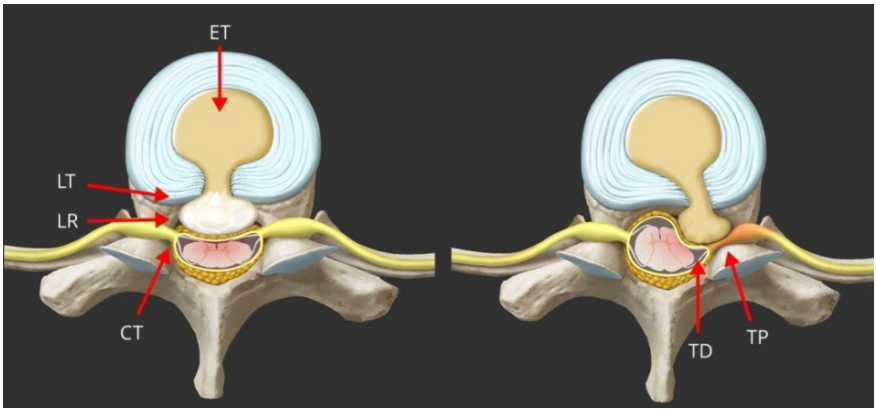

Image 6: Universitätsklinik für Neurochirurgie, Inselspital Bern © CC BY-NC 4.0

Depending on the consistency and location of the disc herniation, surgical procedures may be shaped. On the left, 4 methods that can be applied in calcified central disc herniation are shown.: CT (costotransverse), LR (lateral retropleural), LT (lateral transpleural), ET (endoscopic transthoracic). For the

soft lateral disc herniation on the right, excision of the disc herniation can be performed by 2 additional methods:TD (transdural), TP (transpedicular).

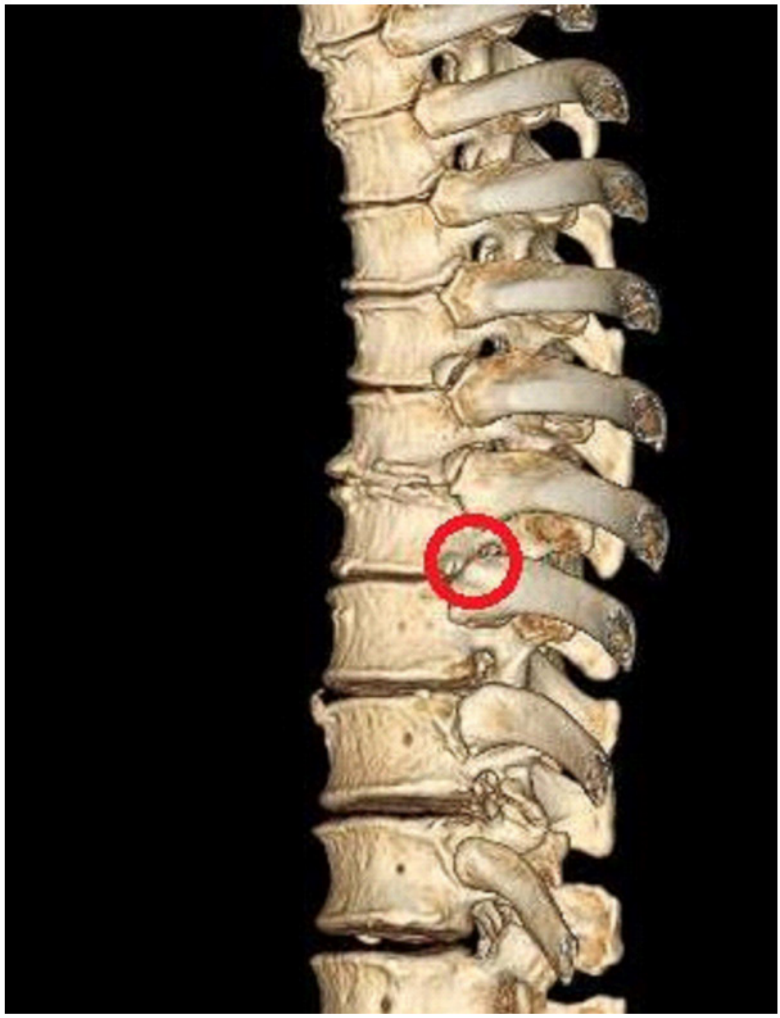

Image 7: In order to reach the disc cavity in the 3D thoracic tomography image, it is necessary to excise the rib head by the amount of area shown in the sign.(22)

12. Result

There are similar complication rates among the anterior and posterior approaches applied in patients with thoracic disc herniation except lung complications. The reason for this is that the posterior pulmonary region is far away, neuromonitoring is applied, and the posterior approach is more

experienced among neurosurgeons. However, anterior approaches are superior to posterior approaches in central, paracentral calcified disc herniations compared to posterior approaches in discectomy. In patients with insectible cases such as kyphosis and deformity, instrumentation can be applied in the same session. Posterior approaches are advantageous in postoperative patient comfort.

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CHAPTER X

LARYNGEAL REINNERVATION

Semra AĞIRBAŞ[1] & Yaser Said ÇETİN[2]

[1] (Asst. Dr.), Van Yüzüncü Yıl University Department of otorhinolaryngology-head and neck surgery
E-mail: semraagirbas@yyu.edu.tr
ORCID: 0000-0003-0932-3116

[2] (Assoc. Dr.), Van Yüzüncü Yıl University Department of otorhinolaryngology-head and neck surgery
E-mail: yasersaidcetin@yyu.edu.tr
ORCID: 0000-0002-7684-4600

1. Introduction

Vocal cord paralysis can have various etiologies including surgery, neoplasia, trauma, radiation, inflammation, and idiopathic reasons. Surgical reasons primarily include thyroid surgery, followed by esophageal, cervical spine, neck, thoracic, and mediastinal surgeries. Vocal cord paralysis can be bilateral or unilateral. Treatment can be performed with medialization thyroplasty, injection laryngoplasty, cordotomy, arytenoidectomy, arytenoid lateralization, and reinnervation.

In patients planned for reinnervation, an extensive evaluation of general condition of the patient, extent of prior surgeries, and cricoarytenoid joint mobility is essential. Additionally, laryngeal pathologies and neuromuscular diseases that may reduce the success of reinnervation should be ruled out.

2. Laryngeal Reinnervation in Unilateral Vocal Cord Paralysis:

Recurrent laryngeal nerve (RLN) injury may occur due to lesions located in the mediastinum, cranium, thorax, neck, or due to surgery. Unilateral vocal cord paralysis causes dysphonia and frequent aspiration. Treatment includes injection laryngoplasty, medialization thyroplasty, and reinnervation.

Primary neurorhaphy can be performed with RLN to restore impaired adduction in unilateral vocal cord paralysis. Nerves such as original RLN, ansa cervicalis (also known as ansa hypoglossi), and hypoglossal nerve can be used as donor nerves. Donor nerve selection may vary depending on the location, size, and causes of injury and previous surgeries.

2.1. Original RLN:

The right RLN leaves the vagus nerve as it crosses inferior to the subclavian artery. It enters the tracheoesophageal groove posterior to the subclavian artery. The left RLN crosses inferior to the aortic arch and progresses into the tracheoesophageal groove. It travels together with the laryngeal branch of the inferior thyroid artery and enters the larynx posterior to the cricothyroid joint.

Chou et al. reported the primary neurorhaphy outcomes of patients who underwent complete RLN transection during neck surgery [1]. Eight patients that underwent primary repair showed improvement in phonation parameters within six months, while the remaining four patients that underwent secondary medialization without repair showed no improvement. The authors recommended primary neurorrhaphy after the detection of a transected RLN during surgery [1].

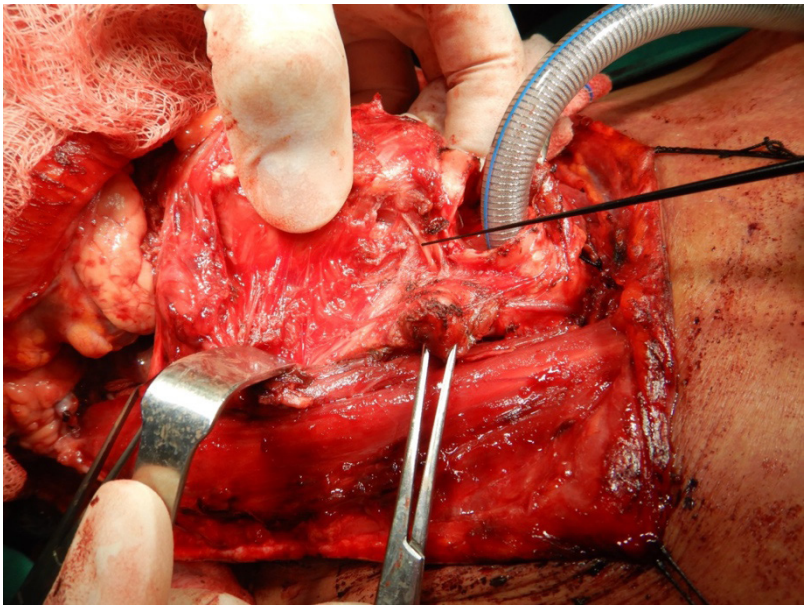

Figure 1. Right recurrent laryngeal nerve (RLN). The image was obtained from the archives of Van Yüzüncü Yıl University Department of otorhinolaryngology-head and neck surgery.

2.2. Ansa Cervicalis:

Ansa cervicalis is a loop formed by nerves branches of the cervical plexus, innervating all the infrahyoid muscles except for the thyrohyoid muscle. Ansa cervicalis is an ideal option since it is easy to identify, close to the surgical site, has minimal donor site morbidity, and is sufficiently large for neurorrhaphy. Prades et al. suggested that the most ideal option for non-selective reinnervation of RLN is the common nerve trunk that innervates the sternohyoid and sternothyroid muscles or the branch of the sternothyroid muscle [2].

Olson et al. reported near-normal voice results in patients with ansa reinnervation [3]. Zheng et al. found that the mucosal wave was recovered after ansa reinnervation in eight patients [4]. May et al. utilized the ansa-nerve muscle pedicle (NMP) method to innervate the lateral cricoarytenoid muscle in patients and reported favorable acoustic results in 95% of the patients [5].

Maronian et al. achieved near-normal voice quality in patients to whom they applied the Ansa-RLN reinnervation method [6]. Lorenz et al. demonstrated the efficacy of clinical reinnervation in 37 patients that underwent ansa cervicalis-to-RLN anastomosis and reported improvement in endoscopic laryngeal examination and perceptual voice quality in 38 patients [7].

Ansa cervicalis-RLN neurorrhaphy provides improvement in the tone and volume of the vocal cords without causing significant abduction or adduction of the vocal cords.

2.3. Hypoglossal Nerve

Hypoglossal nerve provides motor innervation of the tongue muscles excluding the palatoglossal muscle. Since it contains a large number of axons and has minimal donor site morbidity in VII-XII cranial nerve neurorrhaphy, hypoglossal nerve is considered a viable donor nerve for RLN reinnervation.

A study conducted by Panielo et al. evaluated nine patients and reported successful reinnervation with videolaryngoscopy and electromyography (EMG) after hypoglossal nerve-RLN neurorrhaphy. Normal voice quality was recovered and complete glottic closure during phonation was achieved in all patients. Additionally, vocal cord adduction was detected in the patients [8]. In the same study, the authors suggested that an RLN stump with a minimum of a 3-cm diameter is needed for a tension-free hypoglossal nerve-RLN neurorrhaphy. The authors also noted that although this technique can be disadvantageous since it leaves a longer remnant and leads to increased donor site morbidity, it

is advantageous over ansa cervicalis neurorrhaphy since it provides stronger, almost complete reinnervation, appropriate temporal activity, and sphincter-like function on swallowing [8].

3. Laryngeal Reinnervation in Bilateral Vocal Cord Paralysis (Bvcp)

Bilateral vocal cord paralysis (BVCP) may result from thyroidectomy, neoplasms, trauma, or idiopathic causes. It may manifest with various symptoms including dyspnea (67%), stridor (48%), voice distortion (47%), dysphagia and aspiration (19%) [9]. When abduction of the vocal cords cannot be achieved, it may cause life-threatening respiratory distress. Surgical techniques such as posterior cordotomy and arytenoidectomy can be applied to ensure adequate patency of rima glottidis.These methods are destructive methods that affect the sound quality and have a risk of aspiration. Successful posterior cricoarytenoid muscle reinnervation can provide adequate airway patency without the use of destructive methods. Therefore, the phrenic nerve, superior laryngeal nerve, and ansa cervicalis, all of which show phasic activity during inspiration, can be used as donor nerves.

3.1. Phrenic Nerve

In 1983, Crumley performed reinnervation of the posterior cricoarytenoid (PCA) muscle with the phrenic nerve in five patients with BVCP. A mild improvement in glottal opening was observed in four patients in the postoperative period [10].

Li et al. performed bilateral PCA reinnervation with left phrenic nerve graft in 44 patients with BVCP. Unilateral or bilateral vocal cord abduction was achieved in 41 and decannulation was performed in 38 patients [11]. Another study by Li et al. evaluated seven patients in 2019 and the authors achieved decannulation in four patients [12]. Similarly, Lee et al. achieved decannulation in eight pediatric BVCP patients via selective laryngeal reinnervation using the phrenic nerve [13].

Selective laryngeal reinnervation using the phrenic nerve in BVCP is a promising technique due to its decannulation rate and its contributions to the improvement in patients' symptoms. Hemidiaphragmatic paralysis is the most crucial morbidity associated with the use of the phrenic nerve. Fackler et al. evaluated the postoperative respiratory functions of 14 patients that underwent facial reinnervation with phrenic nerve graft and reported that the effect of

unilateral phrenic nerve injury on ventilation capacity was minimal in patients with normal lungs in the preoperative period [14].

3.2. Ansa Cervicalis:

Tucker performed PCA muscle reinnervation with the neuromuscular pedicle technique with ansa cervicalis in 202 patients with BVCP and reported a 74% success rate within a minimum of two-year follow-up [15].

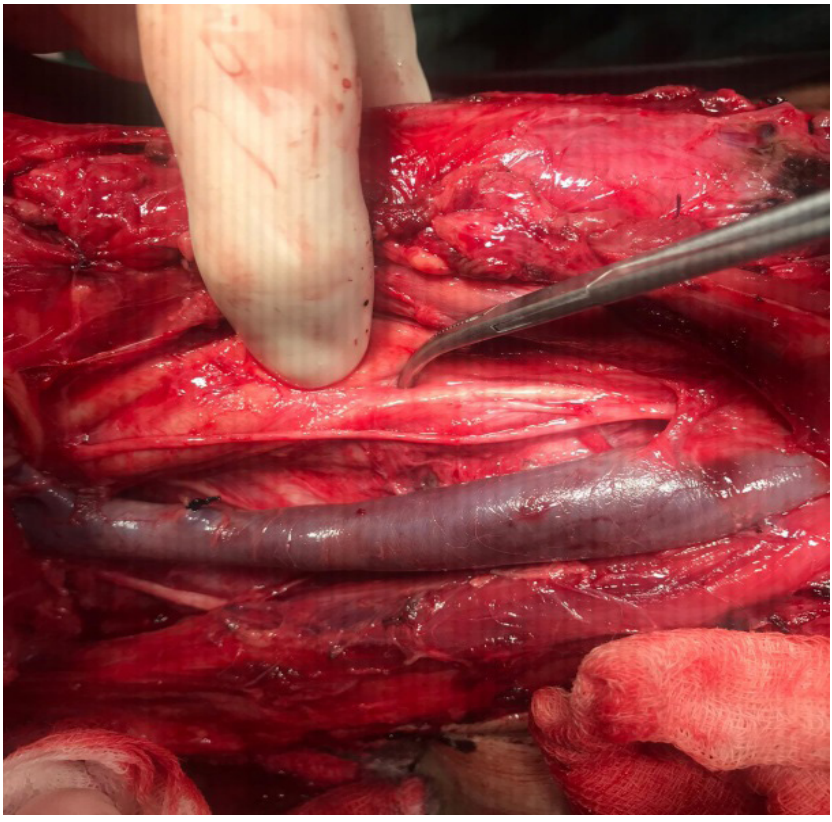

Figure 2. Ansa cervicalis. The image was obtained from the archives of Van Yüzüncü Yıl University Department of otorhinolaryngology-head and neck surgery.

In a study by Zheng et al. that evaluated six patients with BVCP, bilateral PCA muscles were reinnervated with the phrenic nerve and the ansa-NMP technique. Although normal abduction movement was observed on the phrenic side in five patients, no movement was observed on the side reinnervated with the ansa [16]. The success of reinnervation with the phrenic nerve may be correlated with the phasic inspiratory activity of the phrenic nerve.

3.3. Superior Laryngeal Nerve

The superior laryngeal nerve may be preferred for reinnervation due to its activity in respiration, its length, and the number of axons it contains [17]. Orestes et al. anastomosed the external branch of the superior laryngeal nerve to the main trunk of RLN and also performed neurorrhaphy of the ansa cervicalis to the adductor branch of RLN. In these patients, both adequate glottic opening and decannulation were achieved. Although vocal quality was excellent in both patients, speech therapy was required in one of them [18].

4. Sensory Reinnervation of the Larynx

The internal branch of the superior laryngeal nerve is primarily responsible for sensory reinnervation of the larynx. Injury to this nerve may lead to aspiration problems. Aviv et al. performed neurorrhaphy between the great auricular nerve and the internal branch of the superior laryngeal nerve in two patients who suffered from severe post-stroke aspiration pneumonia. Although dysphagia symptoms persisted in both patients after six months, aspiration pneumonia disappeared. Improvement in oral intake was observed in both patients. [19]. Since data on sensory reinnervation are limited, further clinical studies are needed to reach objective conclusions.

In the treatment of BVCP, novel treatment modalities are being investigated in addition to existing modalities such as posterior cordotomy, arytenoidectomy, and reinnervation. New methods that attract attention include botulinum toxin injecting into the adductor and abductor muscles of the vocal cord, neuromodulation, laryngeal pacing and functional electrical stimulation, gene therapy, and stem cell therapies [20]. Accordingly, we hope that novel treatments that have minimal morbidity and restore normal voice quality as well as normal physiological vocal cord movement in BVCP patients will be developed in the future.

5. Reinnervation in Laryngeal Transplantation

Laryngeal transplantation is considered in patients with total laryngectomy to improve their airway and phonation functions. Successful laryngeal reinnervation is vital for increasing the feasibility of laryngeal transplantation. Laryngeal transplantation was first performed by Strome et al. in 1998. After revascularization of the transplanted larynx, direct neurorrhaphy was performed

to both superior laryngeal nerves of the recipient patient and to RLN of the donor patient. In the examination performed at the first month, the vocal cords were in a paramedian position. Improvement in vocal cord movements and oral intake was observed in the fourth postoperative month. However, the supraglottis and glottis were sensitive to tactile stimules and the patient had cough. At six months, the left vocal cord had approached the midline and a significant improvement was observed in the patient's voice. Although the left RLN could not be located during the surgery, the observation of movement in the left vocal cord was explained by spontaneous reinnervation from nonspecific neurons. All voice-related measurements were within normal limits for 3 years. Reinnervation of bilateral thyroarytenoid and cricothyroid muscles was demonstrated by EMG. Approximately 72 months after the surgery, the patient could not be decannulated because the vocal cords remained immobile in the median position [21].

Farwell et al. performed laryngeal transplantation in a 51-year-old patient with laryngeal stenosis who had undergone tracheotomy due to trauma at the age of 11. After the arterial anastomoses, bilateral superior laryngeal nerve and right RLN neurorhaphy were applied. The adductor branch of the donor left laryngeal nerve was sutured to the recipient ansa cervicalis nerve trunk on the left side. After venous anastomoses were made, microneurorrhaphy was performed between the donor RLN and the patient's phrenic nerve on the left side. In the endoscopic examination at 18 months, synkinetic activity and abduction of the vocal cords were observed and the patient could not be decannulated due to subglottic stenosis [22].

6. Results

Laryngeal transplantation is promising for patients whose laryngeal functions are impaired due to cancer or laryngeal injury. Restoration of impaired laryngeal functions by selective reinnervation or laryngeal pacing can significantly reduce the challenges in the feasibility of laryngeal transplantation.

Data on the timing of laryngeal reinnervation are limited. It has been recommended that if RLN injury is detected intraoperatively, it should be repaired immediately; however, when it is not noticed or cannot be repaired, it is recommended to wait for 6-9 months for spontaneous recovery and the effectiveness of compensation mechanisms [23].

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CHAPTER XI

UPPER CERVICAL REGION TRAUMAS

Abdullah Talha ŞİMŞEK

Istanbul Medeniyet University
Faculty of Medicin,Department of Neurosurgery,
E mail: simsektalha@hotmail.com
ORCID: 0000-0002-8668-3935

1. Introduction

Upper cervical vertebrae traumas are traumas with high mortality rates, difficult surgical treatment and therefore follow-up and treatment is very important. Upper cervical traumas are more common in the elderly than in the young. However, these rates may vary according to countries. The atlas bone articulating with the occipital bone condyle and the joint formed by the axis with the atlas, different ligamantous structures, the course of the vertebral artery have caused different fracture types to be seen according to the levels in traumas in the region and different surgical approaches are required. In young people, it is mostly caused by high energy trauma, while in the elderly it is more often caused by low energy trauma due to osteoporosis. Trauma can result in sudden death due to the respiratory and cardiovascular autonomy centres located in the region. In addition, these traumas may be accompanied by skull fractures, cerebral haematomas and abdominal and other vertebral traumas due to anatomical proximity.

2. Occipital Condyle Fractures

Occipital bone fractures are rare fractures that usually occur with high-energy trauma.Anderson and Montesano divided these fractures into three groups.(Figure 1) The most common Type 2 fractures are skull base fractures extending into the occipital condyle Type 1 fractures of the condyle due to compression are seen in the 2nd frequency.There is no ligament damage Type 3 fractures are fractures of the condyle caused by a blow from the opposite

direction with tears in the adjacent alar ligament.In the treatment of fracture types, surgery is performed for Type 3 fractures due to their instability .In the other two fracture types, patients should be followed up with Philadephia type cervical collar.(13,12)

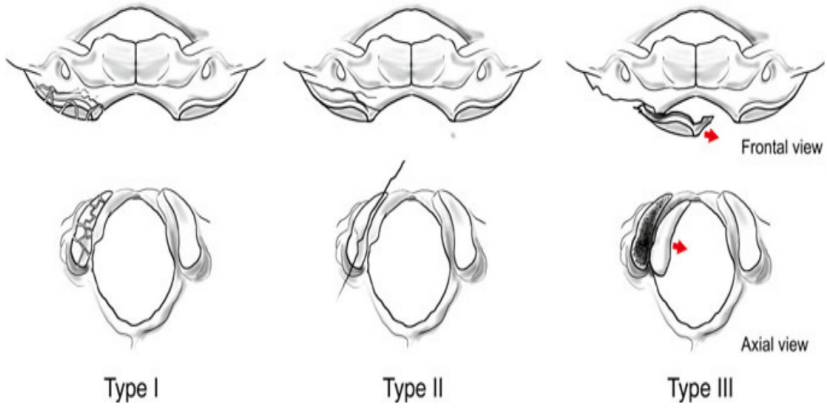

Figure 1: Anderson-Montesano classification

The three types of the Anderson-Montesano classification:type 1 impaction type of fracture;type II more extensile basi-occipital fracture;type III avulsion fracture near the alar ligament

3. Occipitoatlantal Dislocation

The most important ligaments that stabilize this region are the alar ligaments and the tectorial membrane. With hyperextension, the alar ligament may tear with lateral flexion of the tectorial membrane and instability develops . Due to hyperflexion of the Atlas, separation of the posterior elements formed with the Axis is observed. Traynelis classification is used in current treatment. It is divided into 3 types. (Figure 2)

Group 1: It is the displacement of the occipital bone towards the front of the atlas after trauma.

Group 2: Longitudinal distraction of the occipital bone from the atlas

Group 3: It is the displacement of the occipital bone towards the front of the atlas after trauma.

Patient mortality is high after trauma to this region. The number of surviving cases is low. The patient is usually brought to the emergency room with the

absence of spontaneous breathing. Mr and CT should be requested for diagnosis. A hematoma in that area on MRI should suggest occipitoatlantal dislocation. Since the ligament structure is weaker in children than in adults, the damaging effect of traumas in this region is higher. Dislocation can be calculated by Powers ratio.A ratio above 1 indicates dislocation (Figure 3). In the treatment, patients are placed in traction with very little weight. After reaching the normal position, the occipital, C1, C2, C3, C4 instrument is applied. (14,15)

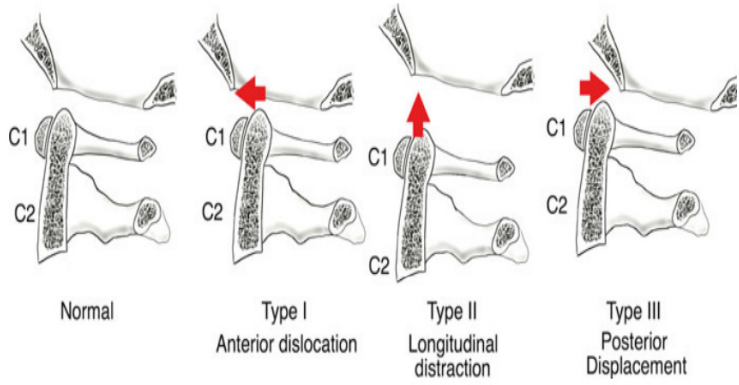

Figure 2: The three types of the Traynelis classification: Type 1 fractures occur when the condyle slides anterior to the atlas.;type II occipital condyles are displaced longitudinally in relation to the atlas; Type 3 fractures result from dislocation of the condyle towards the posterior aspect of the atlas. (1)

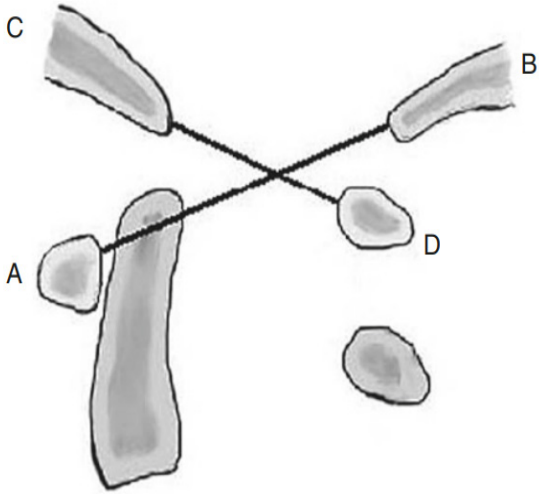

Figure 3: With lateral radiography, shifts in the occipitocervical region, called the Powers ratio, can be detected. CD:Distance from basin to posterior arch of C1.AB: It is the distance of the opistion to the front edge of the atlas.

4. Atlas Fractures

Atlas fractures are fractures caused by excessive pressure of the condyles on the atlas due to compression trauma of the head.The most supportive ligament for stabilisation between the atlas and adjacent structures is the transverse ligament. Whether or not surgery is required may vary depending on the ligament damage. Atlas fractures are divided into 3 (Figure 4).

Type 1: Fracture in one of the anterior or posterior arches of the atlas

Type 2: Fracture of the ring-shaped Atlas in 4 places (Jefferson Burst fracture)

Type 3: These types of fractures are fractures and separations seen in the lateral masses as a result of advanced compression trauma.

While Type 1 and Type 3 are mobilized with a corset, in Type 2, if the transverse ligament is damaged, the head is stabilized with a halo and then fusion is applied.(Table 1) In addition, separation of the lateral masses more than 7 mm indicates transverse ligament damage and is a condition that requires surgery. (6,12)

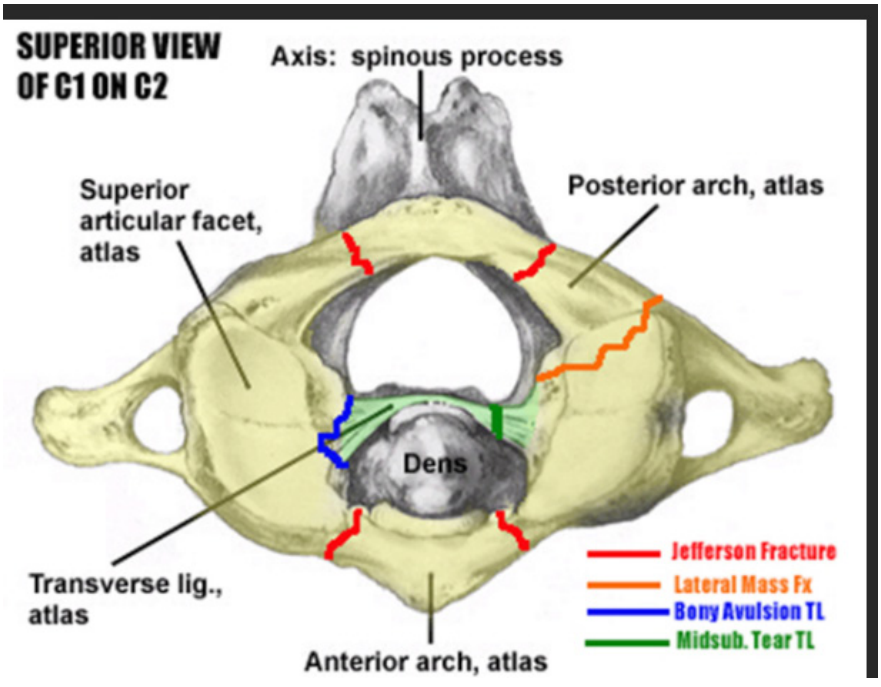

Figure 4: Atlas fractures

Table 1: Atlas Fractures Classification

	Landells Atlas Fractures Classification
Type 1	Isolated anterior or posterior arch fracture. Most common injury pattern "Plough" fracture is an isolated anterior arch fracture caused by a force driving the odontoid through the anterior arch. Stable injury Treat with hard collar.
Type 2	Jefferson burst fracture with bilateral fractures of anterior and posterior arch resulting from an axial load. Stability determined by the integrity of transverse ligament. If intact, treat with a hard collar. If disrupted, halo vest (for bony avulsion) or C1-2 fusion (for intrasubstance tear)(see Dickman classification below).
Type 3	Unilateral lateral mass fx. Stability determined by the integrity of the transverse ligament. If stable, treat with a hard collar. If unstable, halo vest.

5. Odontoid Fractures

Odontoid fractures are seen in 20% of all cervical vertebra fractures. (5). While the rate of neurological deficit due to odontoid fracture is low, 25-40% of cases with odontoid fracture die at the scene due to the severity of trauma. Odontoid fractures often occur with hyperflexion and hyperextension. (11). Today, odontoid fractures are most commonly evaluated using the Anderson and D'alonzo classification. Accordingly, fractures are divided into 3 types.(2).

Type 1: It is an avulsion fracture above the transverse ligament at the apex of the odontoid bone.

Type 2: Fractures seen at the junction of the odontoid process and the spinal body. This is the most common type.

Type 3: In this type, these are fractures occurring in the front and back of the corpus of the odontoid bone.(Figure 5)

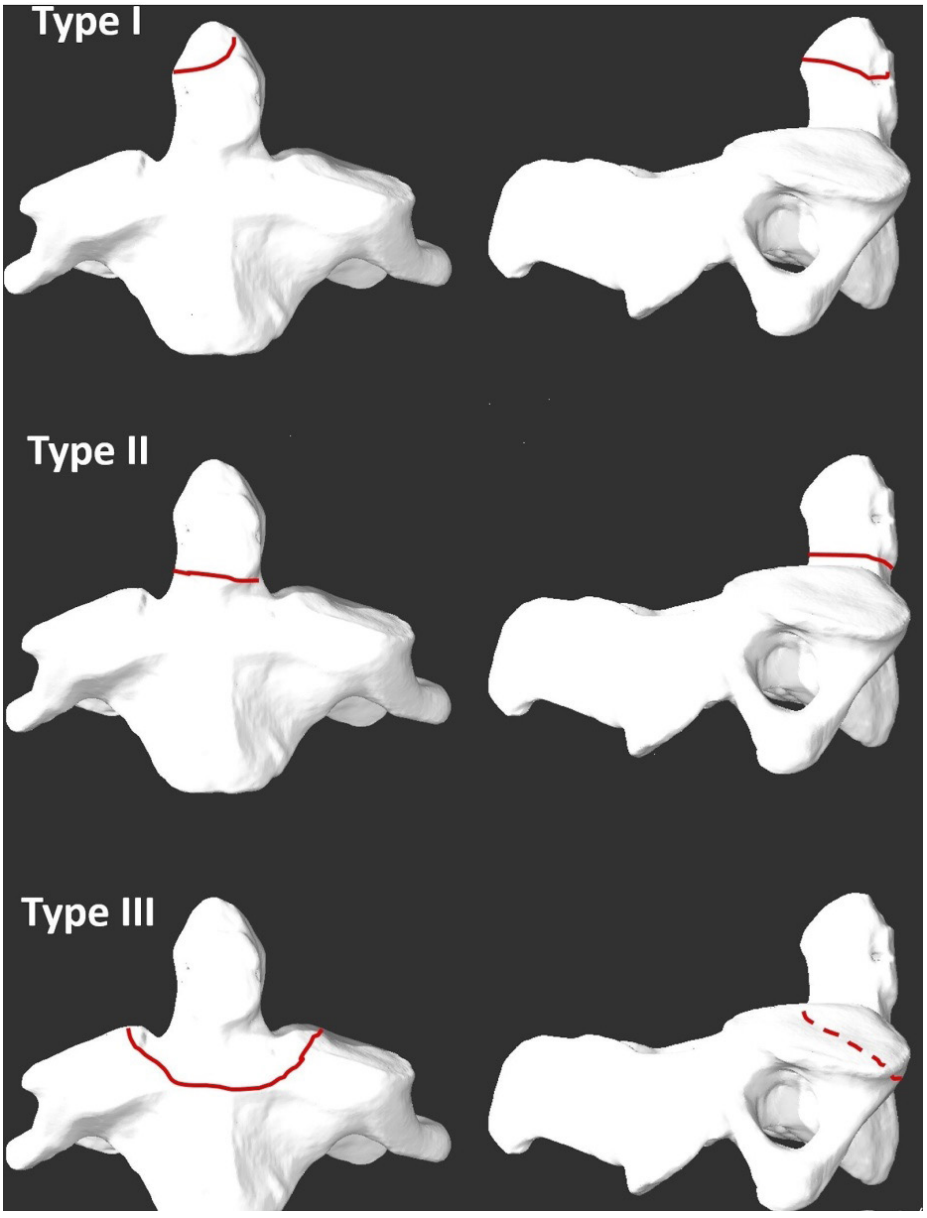

Figure 5: Anderson and D'alonzo classification

Type 2 fractures are the most common type and although their treatment is considered surgical, it is still controversial today. The rate of nonunion is 30% in this type of fractures. These fractures are divided into 3 types by Gauer.(Figure 6) (9)

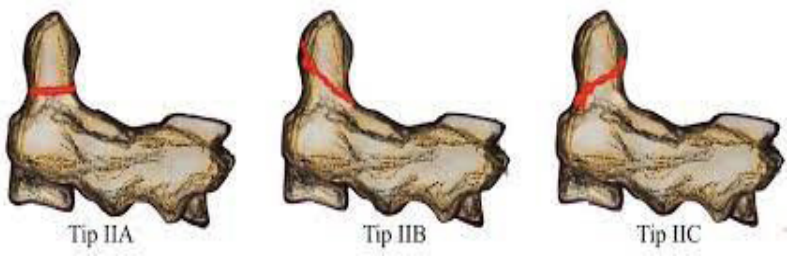

Figure 6: Gauer Classification

(2,4) Type 2 fractures are divided into 3. Type 2A: Non-displaced fractures. They are treated conservatively. Type 2b and 2c fractures are treated surgically. In order to cross each other, respectively; Type 2b is anterosuperior to posteroinferior and type 2c is anteroinferior to posterosuperior fracture types.

Today, odontoid fractures are treated with external immobilization, odontoid screwing, and anterior or posterior transarticular screwing methods. Type 2 and 3 fractures are treated with surgery. There is a risk of non-fusion in type 2 fractures. Type 1 fractures are treated with Halo vest or cervical collar. Among these reasons, the posterior displacement of the fractured fragment, the angulation of the separated fragment being more than 10 degrees, the displacement of the fractured fragment by more than 4-6 mm and another reason for nonunion is being over 65 years old.Surgery is recommended for type 3 fractures due to the risk of nonunion and pseudoarthrosis due to anterior displacement. In other cases, 6-8 weeks of immobilization with a Halo vest and neck brace is sufficient.

6. Atlantoaxial Dislocations (Rotation)

The fact that the ligament structure is newer in children and its flexibility is higher increases the risk in these traumas. Atlantoaxial dislocations are currently divided into 3 groups with the Fielding classification.

Type 1: There is only rotational deformity without displacement.

Type 2: The lateral joints between the two bones slip over each other by 3 mm or more.

Type 3: Normally, the Atlantodental distance is 3.5 mm. The increase in this distance may be due to transverse ligament damage and is called type 3.(8)

However, today the Wang classification is considered more useful as a guide for surgeons. (16)

Table: 2 : Wang Classification

Type	Description	Diagnosis	Incidence (%)	Treatment
I	Instability	Reducible in dynamic X-rays	52.2	Posterior fusion procedure
II	Reducible	Reducible with skeletal traction under general anesthesia	17.7	Posterior fusion procedure
III	Irreducible	Irreducible with skeletal traction under general anesthesia	29.6	Transorally released anteriorly before posterior fusion
IV	Bony dislocations	Dislocations with bony anomalies that are visualized by reconstructive computed tomography scan	0.4	Transoral odontoidectomy

7. Hangman Fractures

Hangman Fracture is so named because it was first seen in the imaging of hanged people. It is also known as traumatic spondylolisthesis of the axis. Today, there is a treatment algorithm according to the Effendi classification. Accordingly, there are three main classifications.(7)(Figure 7,8)

Type 1 fracture: There is a bilateral pars interarticularis fracture. There is less than 3 mm displacement on C2,C3. Treatment is possible with an external collar.

Type 1A: There is a bilateral pars fracture. The fracture extends to the transverse foramen.

Type 2: Fractures with axial loading and hyperextension followed by hyperflexion and displacement and angulation of more than 3 mm.

Type 2A: Injuries caused by flexion and distraction. There is little forward slippage. However, the angulation is high. These types of fractures occur due to tears in the anterior and posterior ligaments.These are unstable fractures. Surgical treatment is required.

Type 3: Due to compression and flexion, the axis shifts anteriorly by 3 mm or more and angulates anteriorly after fracture.Single or bilateral facet dislocation accompanied by Anterior and Posterior Longitudinal Ligament tears are observed.

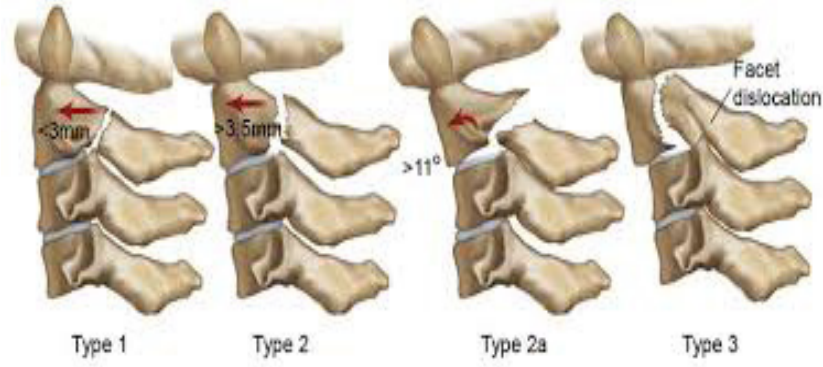

Figure 7: Effendi Classifications

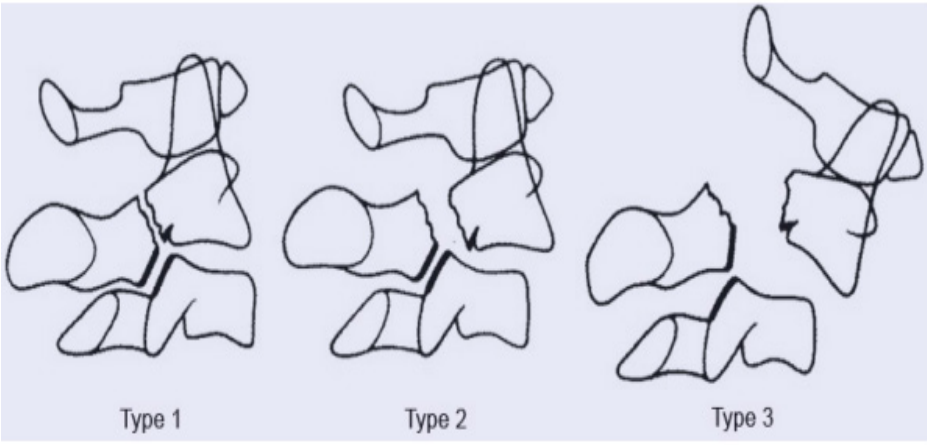

Figure 8: Effendi Classifications

In treatment, external immobilization is mostly applied. Surgical indications include those with cranial fractures due to head trauma, those who cannot use Surgery should be considered in cases of nonunion lasting more than 3 months with halo.Although there are various opinions, Types 1, 2 and 2a can be treated primarily with external mobilization. If there is no fusion, surgery is performed. (10) Type 3 fractures are treated surgically

8. Results

The region known as the upper cervical region is the region formed by the articulation of these bones, including the occipital condyle, atlas, axis bones and the joint between the axis and the 3rd cervical vertebra. In this region,

the vertebrae, together with the ligament structures and intervertebral discs, participate in the movement of the head and neck and anatomically stability the neck. Traumas in this region are vertebral fractures, ligament tears and disc damage that occur with excessive force. With the current classifications made in this region, methods of approaching these traumas have been determined today. While surgery is not required in some cases, surgery is performed in cases with damage that we consider to be unstable. The new treatments will continue evolve with the new development of technology.

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CHAPTER XII

UTILIZING PREHOSPITAL TRANEXAMIC ACID FOR HEMORRHAGE IN TRAUMA CASES

Adem AZ

(Specialist MD), Haseki Training and Research Hospital,
Department of Emergency Medicine, Istanbul, Türkiye
E-mail:adem.aaz@gmail.com
ORCID: 0000-0002-7204-6185

1. Introduction

Trauma is the leading contributor to global mortality, particularly among young adults. (1) Annually, over 45 million individuals experience moderate to severe disability and morbidity due to trauma. (2) Uncontrolled hemorrhaging emerges as the primary factor in trauma-related fatalities. (3) The majority of these deaths occur either at the scene or within the initial four hours of the patient's arrival at an emergency department. (4) The precise mechanisms underlying acute traumatic coagulopathy are not yet fully understood and lack a universally accepted definition. Approximately 20% of trauma patients develop severe hyperfibrinolysis, contributing to elevated mortality rates. (5) Tranexamic acid (TXA), an antifibrinolytic agent, is utilized to mitigate traumatic hemorrhage. (6) Numerous studies have delved into the application and efficacy of TXA in prehospital settings. (6,7,8) TXA is recognized for its ability to reduce mortality rates among trauma patients with hemorrhage. Moreover, it was administered to victims of the Bataclan attack in Paris to reverse trauma-induced coagulopathy and hemorrhage. (9) This section provides a comprehensive overview of the use of TXA in individuals experiencing hemorrhagic trauma, including new evidence regarding the intramuscular route (IM).

2. Tranexamic Acid (TXA)

Tranexamic acid (TXA) is an antifibrinolytic drug used to prevent traumatic bleeding. (6) This molecule was invented by Japanese scientists Shosuke and Utako Okamoto after World War II. (9) Initially, its primary focus in clinical settings was the treatment of patients suffering from bleeding disorders. (9) TXA reduces hemorrhaging by inhibiting the enzymatic breakdown of fibrin blood clots. The mechanism involves competitively binding to the lysine domains of plasminogen and plasmin, preventing their interaction with fibrin and subsequently limiting the process of fibrinolysis. (10) Additionally, empirical evidence suggests that TXA enhances platelet function and inhibits plasmin-induced platelet activation, ultimately promoting clot stabilization and inhibiting thrombogenesis. (11) Beyond their role in fibrinolysis, plasminogen and plasmin serve as pro-inflammatory mediators, playing pivotal roles in initiating cellular and complement inflammatory responses following tissue damage. Through the inhibition of plasminogen and plasmin-mediated inflammation, TXA has the potential to alleviate the intense inflammatory response observed during trauma, thereby contributing to the attenuation of coagulopathy. (10) Consequently, TXA proves effective in reducing traumatic bleeding and mitigating the associated damage resulting from hemorrhaging. (6,11)

3. Role of TXA in Traumatic Hemorrhage

TXA is employed in surgical interventions to reduce hemorrhage and the need for blood transfusion. The CRASH-2 study, the most comprehensive clinical trial conducted to date to assess the efficacy of TXA in managing bleeding trauma patients, revealed that TXA consistently decreased hemorrhage-related fatalities compared to no antifibrinolytic therapy. (13) The CRASH-2 study demonstrated the successful administration and acceptance of TXA without significant concerns about thromboembolic side effects. (13) The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERS) indicated that the intravenous (IV) use of 1 g of TXA reduced mortality rates compared to non-use, particularly in severely injured cases, penetrating trauma, and situations requiring multiple surgical interventions. (14) The CRASH-3 study, investigating TXA administration within three hours of injury in over 12,000 traumatic brain injury patients using the same dosing protocol as CRASH-2, found an association between TXA and reduced head injury-related mortality. (15) Numerous studies confirm that TXA effectively

controls bleeding by preventing or inhibiting the development of coagulopathy. (14,16,17) Moreover, it significantly reduces the occurrence of multiple organ failure. (14,18) A comprehensive analysis, which combines information from approximately 40,000 patients in the WOMAN and CRASH-2 studies, revealed that each 15-minute delay in treatment resulted in a 10% reduction in the survival benefit from TXA therapy. The meta-analysis emphasizes the significance of administering TXA within the first hour and directly at the injury scene. (19) Considering that most bleeding-related trauma deaths occur in the prehospital setting and are likely linked to the rapid onset of hyperfibrinolysis within minutes of injury, the clinical efficacy of TXA justifies its use in treating bleeding patients in the prehospital setting. (10) Additionally, several studies have indicated that TXA is effective when given within the first 3 hours of a traumatic injury. (14,16,17) Furthermore, administering TXA over 3 hours after the injury has been linked to increased morbidity and mortality. (6,16)

4. Safety of TXA Use

Numerous studies confirm the safety of administering TXA at the prehospital scene. (14,16,20,21) These studies did not observe any vascular occlusive side effects related to TXA. (16,21) While some researchers have reported adverse effects after TXA use, they suggest that these incidents may be connected to delays or the failure to employ thromboprophylactic measures. (18,22) Moreover, Roberts et al. demonstrated that the potential complications associated with TXA use are comparable to situations where TXA is not used. (16) Their study found no disparity in the occurrence of vascular occlusive events between those receiving TXA and the placebo group. (16) Consequently, the administration of TXA in the prehospital setting has been found safe by numerous studies.

5. Dose of TXA Administration

Most clinical studies recommend a treatment regimen for trauma patients with hemorrhage in the prehospital setting, involving a 1 g loading dose of TXA followed by a subsequent infusion of 1 g over 8 hours. (14,16,20,21) This regimen is based on a systematic Cochrane review conducted in 2007 regarding anti-fibrinolytic use in surgery. (23) However, the optimal TXA dose for trauma lacks sufficient study. While the 1 g TXA bolus and 1 g infusion protocol are considered a safe regimen, staying below doses that may precipitate a seizure,

questions arise about its appropriateness for various types of trauma outside clinical settings. (11) Nevertheless, current studies recommend the administration of a 1 g IV TXA bolus in the earliest post-traumatic period, followed by a 1 g TXA infusion over 8 hours. (14,16,20,21)

6. Can TXA be Administered by Intramuscular Injection?

Various animal and human studies have demonstrated the effectiveness of TXA through oral, topical, and IV routes. However, the recommended route for TXA is parenteral administration, especially in surgical and trauma patients. (24) In clinical practice, TXA is typically administered as a 1 g IV bolus over 10 minutes, followed by a 1 g infusion over 8 hours. (24) The main challenge in using TXA in the prehospital era is its requirement for IV access. To investigate the feasibility of IM injection, randomized trials were conducted comparing 1 g TXA IV, 1 g TXA IM, and 2 g TXA orally, followed by both in vivo and in vitro pharmacodynamic studies. (25) The findings revealed that IM administration of TXA was well-tolerated and rapidly absorbed. (25) Additionally, in the United Kingdom, paramedics are now authorized to administer IM TXA in pre-hospital environments. (25) Another study compared TXA administration via IM autoinjector or assisted IM route and found that the effectiveness of TXA in controlling bleeding and reducing mortality was not significantly influenced by the route of administration. (26) Research indicates that therapeutic TXA concentrations are achieved within approximately 10 minutes after IM injection, lasting only several seconds. This timeframe is almost faster than IV injection, considering the time demands and the 10-minute administration period for TXA injection via IV. (9) While IV administration is considered the preferred method for trauma and surgery patients, the IM route can be a viable option in situations where obtaining IV access is challenging and in emergencies requiring swift intervention. (9) The use of prefilled syringes for IM TXA injection could ease the burden on emergency services, reduce on-site procedure duration, and lower the occurrence of adverse incidents. (10)

7. Conclusion

TXA has indeed shown promise in enhancing survival rates after trauma by reducing excessive bleeding. Current literature recommends the use of a 1 g IV TXA bolus, followed by a 1 g TXA infusion over 8 hours in trauma patients. The time-sensitive nature of TXA administration, particularly within

the first 3 hours of the traumatic event, highlights the importance of prompt intervention to maximize its effectiveness. The preference for IV administration in trauma patients is understandable, as it allows for a rapid and controlled delivery of the medication. However, the acknowledgment of the IM route as a feasible alternative is crucial, especially in situations where establishing IV access is challenging or time is of the essence in emergencies. This flexibility in administration routes ensures that TXA can be promptly administered, even in resource-limited or challenging prehospital environments. Incorporating TXA into prehospital protocols can contribute to more efficient and streamlined trauma care, potentially improving outcomes for trauma victims.

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CHAPTER XIII

MEDICINAL CANNABIS AND THE ENDOCANNABINOID SYSTEM

Sultan Mehtap BÜYÜKER[1]* & Tuğba PESEN[2] & İbrahim BAHÇEKAPILI[3] & Meryem ALBAYRAK[4] & Md. Shah AMRAN[5]

[1](Asist. Prof), Department of Pharmacy Services, Üsküdar University
E-mail: sultanmehtap.buyuker@uskudar.edu.tr
ORCID: 0000-0002-1344-540X

[2] (Msc.), Department of Molecular Biology,
Graduate School of Sciences, Üsküdar University
ORCID: 0000-0002-9761-138X

[3](Engineer) Faculty of Engineering and
Natural Sciences, Üsküdar University
ORCID: 0000-0002-7242-7914

[4] (Msc.), Department of Biotechnology,
Graduate School of Sciences, Üsküdar University

[5](Prof), Molecular Pharmacology and Herbal Drug
Research Laboratory, Department of Pharmaceutical
Chemistry, Faculty of Pharmacy, University of Dhaka
ORCID: 0000-0001-6207-1240

1. Introduction

The use of parts of the plant and/or bioactive products naturally aproduced by the plant for purposes such as survival and adaptation to the environment, for therapeutic purposes, dates back centuries [1]. The bioactive products found in the plant are called phytochemicals [2]. Plants containing therapeutic phytochemicals and used for drug synthesis are called

medicinal plants [3]. One of the such medicinal plants that has been used for centuries is the *cannabis* plant. The *cannabis* plant is divided into 4 types: *Cannabis indica Lam*, which contains high Tetrahydrocannabinol [THC] and is a drug type; *Cannabis sativa* L., which is a fiber type; *Cannabis ruderalis* Janisch and *Cannabis afghanica*, which have intermediate features [4]. *Cannabis sativa* L. is the most commonly used species by societies

Cannabis sativa is a plant that has been used since ancient times in many fields, especially in health with its rich phytochemical contents. The *cannabis* plant contains hundreds of compounds and phytocannabinoids, terpenes and flavonoids, which are called specific secondary metabolites [5]. As a result of the use of plant parts or products containing these metabolites for medicinal purposes, the plant is called medicinal *cannabis* [6]. THC and Cannabidiol [CBD] phytocannabinoids, which have the most researched and therapeutic effects in the plant, have preserved their therapeutic effects evolutionarily and have an effect on the endocannabinoid system, which is involved in many physiological events in the human body [7].

The endocannabinoid system consists of endogenous ligands, cannabinoid receptors to which ligands bind, and enzymes responsible for the biosynthesis and degradation of ligands [8]. The endocannabinoid system [ECS], a neuromodulatory system, is based on the use of one or more chemicals by a particular neuron to regulate different neuron populations [9]. It affects many physiological events such as energy balance, blood pressure, appetite stimulation, pain, nausea and vomiting, and memory in relation to the homeostasis of the body [10]. It is found in almost every tissue of the body. Although addiction is associated with the pathology of many psychological disorders such as schizophrenia, it has positive effects in the treatment of some diseases such as Alzheimer's, epilepsy, and cancer [11]. The therapeutic effects of *cannabis* on diseases and the investigation of its relationship with the endocannabinoid system are of great importance for the development of *cannabis*-based medicines today.

2. Conventional Use

Cannabis sativa (marijuana/*cannabis*) is a plant of central Asian origin that has been used since ancient times [9]. The plant and its parts have been used by many nations for various purposes until the 21st century. Although it is most commonly used in the form of tea and tincture, the oils obtained from its seeds are nutritious because they contain essential fatty acids such as gamma-linolenic acid and stearidonic acid [12]. About 10,000 years ago, the Chinese used

cannabis for food and fiber [13], the Egyptians for food and medicinal product [14], the Scythians for religious practices [15], and the Greeks for medicinal products [15]. In addition, *cannabis* has an important place in some religions such as Hindu [9] and the fibers obtained from the *cannabis* plant continue to be used in industrial areas today.

The first use of *cannabis* as a therapeutic agent appeared in China around 3000 BC, and its seeds have been used as an analgesic effect in the treatment of constipation, malaria, childbirth, surgery, and pain [16]. Its use as a therapeutic agent in India and Egypt dates back to about 1000 BC, and the flower parts of the plant have been used as analgesic, antispasmodic, and anti-inflammatory [17].

In the 19th century, the use of *cannabis* in many diseases was included in the US Pharmacopoeia [18] and its sale in pharmacies began. It has been used to treat asthma, gout, rheumatism, cholera, hysteria, tetanus, mood disorder, insomnia, and pain [16]. As a result of a published study published in 1857, the recreational use of *cannabis* became more and more common [19]. In the middle of the 20th century, *cannabis* has been removed from the US Pharmacopoeia and added to the list of drugs of abuse because of its psychoactive effects, addiction risk, and various other concerns [18].

3. The Morphology of The Plant

Cannabis sativa is an annual and flowering plant suitable for almost all climates [12]. This wind-pollinated plant is dioecious, but in some cases it can be found monoic [20]. The phytochemical profiles produced by the plant differ in male and female plants, and unpollinated female plants contain higher amounts of product than male plants [12]. For this reason, female plants are preferred in areas such as food, fiber and industry.

Cannabis, one of the short-day plants, when grown commercially, begins to bloom after 2 weeks, regardless of the day length [12]. This plant can be grown as drug or fiber type according to its purposes [21] and different morphological features are seen in these plants. The flowering parts are preferred for the plants grown for drug use [21]. The delta-9-tetrahydrocannabinol (Δ^9-THC/THC) molecule is found in greater amounts in the flower parts and is used recreationally or medicinally [21]. Plants grown in fiber type are tall and unbranched, and stem-flower parts are preferred [12, 22]. Compared to THC, cannabidiol (CBD) and other compounds are more abundant and used in industry, food and textiles [22].

Cannabis refers to all bioactive components extracted from plants belonging to the cannabaceae family or parts of plants such as flowers, seeds,

stems and dried leaves [23]. There are approximately 500 compounds in plant parts, including cannabinoids, terpenes and flavonoids, which are secondary metabolites produced by the plant for defense purposes [5,12]. These secondary metabolites, which are more synthesized in female plants, are secreted as a sticky resin at the ends of the trichomes, which are also called glandular hairs, located around the flowers [9].

According to the cannabinoid profiles in the content plants are divided to 5 chemoptypes that are; plants containing more drug-type plants with higher THC content are chemotype I, plants containing fiber and drug-type intermediate properties are chemotype II, plants containing high amounts of CBD and non-psychoactive components are chemotypes III and IV, and finally are fiber type containing rare cannobinoids as chemotype V [20].

4. Plant Taxonomy

Figure 1. *Cannabis sativa*

Kingdom:	Plantae
Ordo:	Urticales
Familya:	Cannabaceae
Genus:	*Cannabis*
Species:	*Cannabis sativa*
Binominal nomenclature:	*Cannabis sativa* L. [24].

5. Plant Phytochemistry

Cannabis sativa has a complex chemical composition consisting of carbohydrates, fatty acids and esters, amides, amines, phytosterols and phenolic compounds, cannabinoids, terpenes and flavoids.

Phytocannabinoids, also known as terpenophenol, are a 21-carbon alcohol compound with a lipid backbone [8]. More than one hundred cannabinoids have been isolated and identified in *cannabis* which contains about 500 compounds [25]. These compounds are biosynthesized from cannabigerolic acid (CBGA), the precursor of all cannabinoids, in the form of carboxylic acid in the *cannabis* plant.

Phytocannabinoids are divided into 11 categories. Drug-type plants contain more Δ^9-tetrahydrocannabinolic acid and Δ^9-tetrahydrocannabinol, while fiber-type plants contain acid forms (cannabidiolic acid [CBDA] and cannabigerolic acids [CBGA]), cannabinoic acids and decarboxylated forms of these acid forms (cannabidiol [CBD] and cannabigerol [CBG]) are more commonly found [20]. Cannabinoids such as cannabichronous acid (CBCA), cannabichrome (CBC), cannabinolic acid (CBNA) and cannabinol (CBN) are present in lesser amounts [20]. Although the chemical properties of phytocannabinoids are almost the same, they create pharmacologically different effects.

Terpenes, another compound found in the plant, are responsible for the formation of plant-specific taste and odor [9]. Terpenes are synthesized from the glandular hairs of the plant and can be found in the root and other parts of the plant as monoterpenes and sesquiterpenes [26]. The most commonly found terpenes are α-pinene, β-myrcene, limonene, β-cariophilene, and linalool [9]. While monoterpene β-myrcene has anti-inflammatory, analgesic, and anxiety and fear-relieving effects, β-cariophilene, a sesquiterpene, has inflammation-reducing and cytoprotective effects [26]. Terpenes can bind to endocannabinoid receptors and act directly or indirectly, as well as changing the duration and mode of action of drugs [27].

Another of the secondary metabolites in the *cannabis* plant is flavonoids, and it is present in the plant as many flavones and flavonols [28]. Cannaflavin A and B, typically identified in the plant, are methylated isoprenoid flavones [28]. Like other secondary metabolites, it has preventive and reducing effects on inflammation, neuron damage and protection against cancer [26]. Cannaflavin A and B show anti-inflammatory and antileishmanial effects, additionaly cannaflavin A has antioxidant and cannaflavin B antimicrobial effects [7-8,19].

Although the molecular targets of cannaflavin A and B are microsomal prostaglandin E2 synthase and arachidonate 5-lipoxygenase, compared to the cannabis-specific phenolic canniprene, canniprene appeared to be less effective in inhibiting mPGES-1 and more in inhibiting 5-LOX [27]. In addition, flavonoids can change the effect of THC by inhibiting hepatic P450 enzymes [26].

6. Medicinal *Cannabis*

Although there is no definite definition, medicinal *cannabis* is defined as "the use of the mentioned metabolites for therapeutic purposes in reducing the symptoms of a disease or in the treatment of diseases" [6]. Today, the compounds produced by the *cannabis* plant are used due to their therapeutic effects such as anxiolytic, analgesic, antipsychotic, antiemetic, antiepileptic, anti-inflammatory and anticonvulsant in reducing the symptoms of patients with many diseases such as dentistry, oncology, chronic pain, psychological disorders, epilepsy and in the treatment of other diseases [29,30].

The difference between the *cannabis* plant and medicinal *cannabis* is based on the molecular forms they contain. While biomolecules in the regular *cannabis* plant are synthesized in the form of carboxylic acid, in medicinal *cannabis*, the biomolecules undergo decarboxylation and turn into their neutral forms with external factors such as heat, light, and extraction after the harvest of the plant, and these neutral forms are used for medicinal purposes [31].

7. Endocannabinoid System

The endocannabinoid system, which has been protected during the evolutionary process for millions of years, includes specific binding sites to endocannabinoids that have been found in the lymphocytes of invertebrates and microglial cells in the central nervous system [32]. ECS is also commonly found in the nervous system, internal organs, connective tissues, glands, and immune cells in the human body [6]. ECS is a neuromodulatory system that affects many physiological events related to body homeostasis [9]. During the disease process, it has been found that there is a relationship between ECS and the pathology of diseases such as cancer, epilepsy and Alzheimer's.

The endocannabinoid system consists of G protein-linked CB1 and CB2 receptors, lipid-structured endogenous ligands (anandamide and 2-AG) with affinity to the receptors, and enzymes involved in the production and destruction of ligands.

7.1 Endocannabinoid Receptor Agonists

Cannabinoids are lipophilic endogenous substances that act by binding to receptors in the endocannabinoid system in the human body [7]. According to the sources they are produced, cannabinoids are divided into three categories; phytocannabinoids synthesized as secondary metabolites in plants, endocannabinoids synthesized in the body in mammals and synthetic cannabinoids that are man-made [19].

THC and CBD, the two main molecules that are naturally produced, most researched among lipophilic cannabinoids and abundant in plants, are terpenophenol with the same formula ($C_{21}H_{30}O_2$) containing 21 carbon atoms, 30 hydrogen atoms and 2 oxygen atoms [33]. These compounds, with molecular weights of 314.45 and 314.46 g/mol, respectively, contain a cyclohexene ring, an aromatic phenolic ring, and a pentyl side chain, while THC contains an extra cyclic ring [34]. Both molecules are synthesized into their acidic form before CBGA by THCA and CBDA synthase enzymes. Subsequently, plants undergo decarboxylation under the influence of heat and light after aging or harvesting, and phytocannabinoids are converted to their neutral forms, THC and CBD [31]. Extracted THC is the main psychoactive substance of the *cannabis* plant [35]. THC, which crosses the blood-brain barrier easily, can accumulate in the liver, heart, spleen and adipose tissues and be stored for a long time, as well as being in high amounts in the brain [36,37]. THC binds to the Cannabinoid type 1 receptor (CB1) and Cannabinoid type 2 receptor (CB2) in the endocannabinoid system, as a partial agonist, and interacts directly with their orthosteric sites [38,39]. CBD interacts with other enzymes and receptors in the endocannabinoid system and cannot directly interact with its specific receptor, CB1 [40]. Due to this indirect interaction, CBD has no intoxicating properties and plays a role in reducing the side effects of THC.

After the discovery of compounds in *cannabis*, synthetic cannabinoids were developed by modifying the structure of THC, one of the main phytocannabinoids of *cannabis*, to form compounds containing bicyclic cannabinoids and aminoalkylindoles [19,41,42]. In addition, pharmaceutical companies have developed synthetic cannabinoids for the treatment of diseases such as cancer and depression [19]. However, these cannabinoids have been abused for recreational purposes and as drugs because they contain psychoactive THC. Synthetically produced and abused type of *cannabis* is called “Spice” and “K-2” in the market [19]. The use of *cannabis* among young people produces

long-term adverse effects [43], [44]. Users are at increased risk of developing *cannabis* use disorder (CUD) and subsequently other substance use disorders (SUD), and as a result of frequent use, mental health problems such as learning and memory problems, psychological problems such as dissatisfaction and behavioral disorders and various health problems [45].

Endocannabinoids naturally synthesized in mammals exist as unsaturated fatty acid ethanolamides, glycerol esters or arachidonoyl glycerol and bind to receptors in the endocannabinoid system in the body [46]. These endocannabinoids with lipid structure include arachidonylethanolamine (anandamide and AEA), 2-arachidonoylglycerol (2-AG), 2-arachidonylglyceryl ether (noladine ether), N-arachidonoyl dopamine (NADA) and virodhamine (OAE) [45]. Anandamide and 2-AG are two of the most studied endogenous ligands, and these ligands are enzymatically regulated. Anandamide, one of the two main endocannabinoids, was isolated from the pig brain in the late 20th century [47] and was found to be associated with regulation of energy balance and many pathologies[48]. Anandamide, which is a partial agonist to Type 1 (CB1R) and Type 2 endocannabinoid receptor (CB2R) [49], acts as a transient receptor potential vanilloid 1 (TRPV1) and G-protein-dependent receptor-55 (GPR55) agonist, indirectly affecting the endocannabinoid system [50]. 2-AG, which is a full agonist to CB1 and CB2 receptors, is also an agonist to aminobutyric acid-A (GABAA) receptors, which are not the main receptors of the endocannabinoid system [51]. 2-AG, which has many physiological functions such as synaptic plasticity, is more abundant in the brain and spinal cord than anandamide [52]. Despite these differences, the common features of the two cannabinoids are that they have similar 3D structures and they are arachidonic acid precursors [49]. When it is necessary these cannabinoids are synthesized from the plasma membranes of cells and released into the extracellular spaces [6,8]. As a result of their release, they act as retrograde (preventive feedback messengers) signaling molecules [53]. It affects the feedback mechanism by playing a role in overstimulation or reducing/ending the activities of enzymes [54].

7.2 Classical Cannabinoid Receptors

Cannabis contains phytochemicals from classical cannabinoid receptors in the endocannabinoid system of the mammalian body and it acts pharmacologically by binding to the Type 1 cannabinoid receptor (CB1R) or the Type 2 cannabinoid receptor (CB2R). In addition, it shows its pharmacological

effects by binding to new cannabinoid receptors, G protein-dependent receptors (GPCR), or transient receptor potential (TRP) channels, without interacting with endocannabinoid receptors.

In 1990, the CB1 receptor, which is synthesized by the CNR1 gene in the endocannabinoid system and consists of 473 amino acids in humans, was cloned for the first time [8]. In 1993, the CB2 receptor consisting of 360 amino acids synthesized by the CNR2 gene was cloned [8]. These two types of receptors belong to the family of G protein-coupled receptors. CB1 from these receptors is found in almost all organs and it is mostly found in the brain, gastrointestinal tract, neuronal tissue and central nervous system and is secreted from peripheral or central neurons in this system [8,49]. Activation of this receptor inhibits GABA and glutamate release and increases potassium and calcium ion channel activity [55]. The CB2 receptor is mostly found in B lymphocytes, macrophages, mast cells, natural killer cells found in the immune system, and lymphoid organs such as the thymus, spleen, and tonsils [8,49]. As a result of the activity of the CB2 receptor, Gi alpha subunit (Gαi) binds to G protein subunits and lowers intracellular cyclic adenosine monophosphate (cAMP) levels by inhibiting adenyl cyclase activity. [19]. Although CB2R is secreted from the central nervous system like the CB1 receptor, they are mainly secreted from immune system cells.

The crystal structures of endocannabinoid receptors were elucidated by forming complexes with both agonist and antagonist compounds. The antagonists AM6538 and tarabanant were used to elucidate the inactivation structure of the CB1 receptor [56]. CB1 receptor contains seven transmembrane helices (TM), 3 extracellular loops (ICL) and 3 intracellular loops (ECL) connecting transmembranes, an extracellular N-terminal and an intracellular C-terminal, and this receptor can exist as a homodimer, heterodimer, or hetero-oligomer [55]. The binding site on the receptor consists of the binding pocket gap by the TM bundle, the direct binding site by the extracellular loop, or the extracellular loop and the binding site gap residues [55]. Besides this binding site, it has an allosteric modulator binding pocket. The proximal N-terminus of the receptor joins the ligand-binding pocket while covering the orthosteric region to inhibit extracellular ligands [56]. With the binding of agonist ligands, the receptors undergo a conformational change and activate the G protein on the intracellular surface which in turn activates certain intracellular signaling pathways.

The active nature of the CB1 receptor has been found to be complex with AM11542 and AM841 agonists, inducing the inward movement of TM1, TM2,

and TM7 [57]. When agonists bind to the CB1 receptor, the F200 residue forms van der Waals interactions with the agonist, while the W356 residue is pulled away, disrupting the twin-switch key interaction with the other residue [56]. As a result of this disturbance, W356 moves inward, while P358 moves outward; thereby reducing the energy required for the outward movement of TM6, which helps in binding the G protein [58,59]. When the active and inactive states of the receptors are compared; inducing the extracellular domains of TM1 and TM2 into the cell, and inducing the outward movement of the TM6 intracellular portion produced a 53% reduction in orthosteric pocket volume, a change in the orientation of residues F170, F174, F177 and H178, with which agonists interact directly, It has been found that the ligand binding pocket is covered by contacting the proximal N-terminus, and as a result of this decrease, the interaction of the agonists with the residues at the N-terminus is further reduced, and this region exhibits a wide conformation [56].

Although the antagonist-inactivated CB2 receptor is similar in structure to CB1, the TM1 and TM2 extracellular portions differ. Unlike the V-shaped ring in CB1 that enters the binding pocket and forms at the closure of the orthosteric region, CB2 in the complex with the AM10257 antagonist remains elongated without directly joining the antagonist binding site and interacts directly with the orthosteric binding site. Another important difference between CB1 and CB2 is W258, which is a highly conserved toggle switch residue in GPCRs belonging to the rhodopsin family. While the CB2R and AM10257 complex restricts the movement of TM6 out of the cell, interacting directly with the twin toggle switch residues and limiting the chain of this residue, in the AM6538 and CB2 complex the ligand cleaves TM1 and TM2 from each other and locks F200 CB1 in an inactive state to restrict dW356 movement [55].

7.3 New Cannabinoid Receptors

CBD, which has low or no affinity for CB1 and CB2 receptors, has pharmacological effects as well as transmembraned ion channel transient receptor potential channels TRPV1, TRPV2, TRPV3 and TRPV4 belonging to the vanilloid subfamily, TRPA1 belonging to the ankyrin subfamily, and anti-inflammatory effects through the TRPM8 receptors of the melastatin subfamily. It can show its inflammatory, antihyperalgesic, antioxidant and analgesic effects as a result of desensitization of the channels by allowing calcium and magnesium ions to enter the cell [60,61]. These channels, whose main task is to regulate body

temperature, to control thermal pain and toxic stimuli, are found in many tissues such as the brain, heart, kidney, and intestine, and they play an important role in the treatment of diseases such as inflammation, pain, neurological disorders and cancer [62]–[64]. The effect of CBD on TRPV1 and TRPV2 receptors has been studied and it has been found that low activity on the TRPV4 receptor, agonist effect on the TRPA receptor, and antagonist effect on the TRPM8 receptor, but its pharmacological effect on TRPV3 receptor has not been studied.

Orphan G protein-dependent receptors (oGPCR) are a family of known endogenous ligands. E-Endocannabinoid-related receptors can be divided into two categories as new cannabinoid receptors (GPR55, GPR18, GPR199) and possible cannabinoid receptors (GPR3, GPR6, GPR12, GPR23, GPR92).

The GPR55 receptor, synthesized from the GPR55 gene in humans and cloned in 1999, is involved in the release of calcium, regulating cancer, neuropathic pain, angiogenesis, GIS, inflammation and inflammatory processes, intracellular signaling (signaling of RhoA, ROCK, ERK and p38 mitogen-activated protein kinase pathways) and transcription factors (NFAT, NF-kB, cAMP, CREB, ATF-2) [65–67]. It has very low homology to CB1 and CB2 receptors and has been proven to perform heteromerization with classical cannabinoid receptors to affect its function [68,69]. Cannabinoid or cannabinoid ligands such as THC, 2-AG, AEA, rimonabant, HU210, and AM251 can activate the GPR55 receptor, although they do not have binding parts for cannabinoids as at the CB1 and CB2 receptors [70]. Discovered in 1997, GPR18, which is synthesized in humans at a length of 331 amino acids by the GPR18 gene, and its other name is the N-arachidonyl glycine (NAGly) receptor, is found in lymphoid organs and tissues such as the spleen, thymus, appendix, lymph nodes, and small intestine. NAGly, abnormal CBD, THC, AEA, arachidonylcyclopropylamide (ACPA) and O1602 show full agonism, while CBD and AM251 show weak partial agonist or antagonist activities [50]. GPR119, which was accepted as a cannabinoid receptor in 2006, is an orphan receptor found in the pancreas and gastrointestinal system, providing energy balance in the pancreas, and playing a role in the regulation of type 2 diabetes, obesity and metabolic disorders [21]. This receptor is activated by natural and synthetic cannabinoids such as oleoylethanolamine (OEA), 2-AG, PSN75963 and AS1269574. Although GPR3, GPR6 and GPR12 sequence similarities are high among possible cannabinoid receptors in the brain and reproductive system, it has been determined that only GPR3 and GPR6 are activated by the endocannabinoid CBD [71,72].

7.4 Endocannabinoid System Enzymes

Of the two most studied cannabinoids, AEA and 2-AG are composed of esters and amides of long-chain polyunsaturated fatty acids; It is biosynthesized on demand and subsequently degraded in response to increased intracellular Ca^{2+} or activation of the phospholipase C pathway of phospholipids at the plasma membrane level [19]. The enzymes involved in the endocannabinoid system perform the production and destruction processes of these endocannabinoids.

Anandamide biosynthesis occurs via multiple pathways, but the most studied major biosynthesis pathway is the pathway by which the enzyme N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) catalyzes N-acylphosphotidylethanolamine (NAPE) anandamide [73]. Other pathways catalyzed by anandamide are as follows: Hydrolysis of NAPE to phosphoanandamide by the phospholipase C enzyme, followed by dephosphorylation of anandamide with phosphatase (PTPN22), conversion of NAPEs to glycero-p-AEA by the enzyme α/β-hydrolase 4, followed by the enzyme glycero-p-AEA and glycerophosphodiesterase 1 phosphodiesterase. hydrolysis of anandamide to anandamide by the enzymes lyso-PLD, glycerophosphodiesterase-4 (GDE4) and glycerophosphodiesterase-7 (GDE7) of N-acyl lysophosphotidylethanolamine (lyso-NAPE) [74–76]. In the deactivation of anandamide, arachidonic acid-derived fatty acid amide hydrolase (FAAH) located in the postsynaptic neuron is involved [77,78]. In addition, cyclooxygenase-2, lipoxygenases and cytochrome P450 monooxygenases also deactivate anandamide by oxidation [79,80].

Although 2-AG biosynthesis also involves more than one pathway, the two most studied pathways are diacylglycerol (DAG) and phosphatidylinositol-phospholipase C-expressed pathway [46]. DAG-lipase enzyme or phospholipase C enzyme with α and β two lipases, which are mostly found in neurons and expressed in the immune system, hydrolyzes DAG to 2-AG molecule [19]. Its deactivation occurs by the enzyme monoacylglycerol lipase (MAGL), which performs glycerol and arachidonic acid hydrolase. In addition, FAAH plays a lesser role in the degradation of 2-AG in the enzymes serine-hydrolase α-β-hydrolase domain 6 (ABHD6) and serine-hydrolase α-β-hydrolase domain 12 (ABHD12) to form glycerol and arachidonic acid [46].

7.5 Allosteric Modulators

Allosteric modulators are ligands that change the configuration of the receptor by interacting with the allosteric regions of the receptors and increase

or decrease the activity of the ligand in the orthosteric region as a result of this change [81]. They show various effects on the orthosteric ligand and are divided as positive allosteric modulators (PAM), negative allosteric modulators (NAM), and neutral allosteric ligands (NAL) [82]. These modulators play an important role in reducing the psychotropic and psychiatric side effects caused by ligands binding to orthosteric sites.

For the CB1 receptor, new ligands that bind to the allosteric site, PAMs such as PAM11, ZCZ011, RTI-371, Lipoxin A4, and negative allosteric modulators such as Org27569, PSNCBAM, ABD1027, GAT358, pregnenolone, CBD, and fenofibrate have been developed [83]. One of the most studied modulators, Org27569 has shown in its characterization as positive allosteric modulators of agonist affinity, while as negative allosteric modulators in the efficacy of agonists [82]. This molecule inhibited agonist-induced G protein-mediated inhibition of cAMP production, while increasing agonist-induced ERK1/2 activation [84]. In addition, CBD plays a role as NAM in the interactions of 2-AG and THC with CB1 receptors and in reducing PLCβ3 and ERK1/2 phosphorylation.

The CB2 receptor has fewer allosteric modulators than CB1. The pepcan-12 molecule, which acts as NAM for CB1, shows PAM for the CB2 receptor [82]. In addition, β-caryophyllene, which is an agonist to the CB2 receptor, also appeared to play a role as NAM [81].

8. Therapeutic Effects of Medicinal *Cannabis*

8.1 Analgesic Effect

Medicinal *cannabis* shows an analgesic effect in the treatment of pain in many areas such as dentistry, cancer and orthopedics.

Chronic pain occurs as a result of acute pain lasting at least 3 months and it is a pain that significantly affects the quality of life and is seen with many diseases such as diabetes, cancer and arthritis. In chronic pain, which is a complex process, patients' complaints may continue when treatment with existing drugs is applied. Therefore, new therapeutic agents are sought for existing drugs. chronic pain; It is divided into three categories: nociceptive pain, neuropathic pain, and nociplastic pain. Pain receptors known as nociceptors, are constantly activated by increased brain activity, creating nociceptive pain [40]. This type of pain caused by tissue damage; calcification, pain arising from internal organs, temporomandibular joint disorder, cancer and back pain are encountered [40]. Rather, it results in immune cells secreting many cytokines (e.g., histamine, serotonin, prostaglandin, bradykinin) in damaged tissue and

carrying damage signals from peripheral nerve fibers to the cerebral cortex [16]. Neuropathic pain; it is the pain that occurs as a result of a lesion or disease in the glial cells of the brain. HIV, diabetes, herpes, chemotherapy-induced back pain, amputation pain, post-stroke spinal cord injury, multiple sclerosis and carpal tunnel pain cause neuropathic pain [40,85]. Wallerian degeneration occurs as a result of degeneration of the axon or myelin sheath and axonal damage to the peripheral nerve [86]. As a result, a large number of proinflammatory cytokines (eg, interleukins, such as tumor necrosis factor α), inflammatory mediators (eg, bradykinin and prostaglandins) and growth factors (eg, nerve growth factor, NGF) are released, resulting in hyperalgesia and allodynia [87]. Nociplastic pain, on the other hand, is related to increased sensitivity of glial cells in the nervous system, although it is unclear whether there is damage to the nervous system [88]. Fibromyalgia, irritable bowel syndrome and low back pain, which cause general muscle pain and soft tissue rheumatism, constitute such pain [9]. Although compounds such as opioids and gabapentinoids are used in the treatment of pain, the effects of these compounds are limited since the CB1 receptor, where cannabinoids show agonist properties, and mu receptors, which opioids show agonist properties, are located in the same region in the treatment of these three types of pain [40]. According to studies, patients may continue to have pain despite the use of opioids. For this reason, there has been a trend towards THC and CBD compounds, which have analgesic effects and cause exogenous activity in pain treatments. Unlike opioids, these compounds do not cause sensitivity to pain (hyperalgesia) after prolonged use [89] and do not cause fatal consequences in overdose (except in patients at high risk of heart attack) [90].

Cannabis sativa is a plant used thousands of years ago in the treatment of various oral and dental diseases, especially toothache. With the discovery of the presence of cannabinoid receptors in the mouth, there has been a trend towards *cannabis*-based products. Although the mechanisms of pain caused by various injuries such as infection and irritation occurring in and around the tooth are not yet clear, it has been found that exogenous cannabinoids are associated with pain management by the presence of endocannabinoid receptors in the salivary glands and receptors such as endocannabinoid-sensitive TRPV1, TRPV2 [91–93]. As a result, in addition to pain, there are oral sprays, mouthwashes, pills, capsules, gum and dental fillings containing CBD for oral hygiene, oral hygiene with anti-microbial, anti-inflammatory and antiseptic effects associated with oral and dental health [30].

Presence of CB1 receptors that play a role in the formation of cancer-related nociceptive pain by affecting the hippocampus, cerebellum, basal ganglia and related corticol regions in the brain; It has allowed the therapeutic effects of medicinal *cannabis* to be investigated in cancer-related manifestations [7]. This receptor is also thought to act synergistically on opioid receptors and other cannabinoid receptors used in the treatment of pain [94]. Although opioids are given to cancer patients as pain relievers in pain management, it has been revealed that these opioids do not show their analgesic effects in some patients. Studies have shown that THC and CBD given to cancer patients for pain management have positive effects and act as pain relievers. In pain treatments, nabiximol, whose trade name is Sativex, containing THC/CBD with equal proportions, Bedrocan tea, a THC/CBD mixture containing high THC, or oral sprays containing only THC, dronabinol or nabilone have shown analgesic effects [95]. These drugs have also been found to reduce both pain and current opioid use. These studies show that THC can be used as an alternative to current treatments in alleviating cancer-related pain.

The use of *cannabis* plant in the treatment of pain experienced as a result of various orthopedic disorders or after orthopedic surgeries has been investigated. Although there is limited evidence in the orthopedic field, it has been reported that *cannabis* used by patients undergoing knee and hip arthroplasty without a prescription relieves pain and reduces their opioid use [96]. In addition, it has been reported that *cannabis* applied in orthopedic procedures such as major joint arthroplasty and femoral fracture fixation reduces the mortality rate [97]. However, an increase in the side effects of *cannabis* applied in knee and hip arthroplasty has been observed in people with cardiovascular disease or at high risk of heart attack [96]. More studies are needed in the field of orthopedics.

8.2 Anticonvulsant Effect

As a result of excessive and uncontrolled electrical discharges of neurons in the brain, seizures related to epilepsy occur, resulting in cognitive and sensory changes in the person [98]. The changes that occur as a result of these seizures may be sudden and temporary, may have a one-time effect or may affect the person throughout his/her life.

Persistent epilepsy arises as a result of the fact that the drugs available in the market are not sufficient to reduce epileptic seizures [99]. The anticonvulsant effects of *cannabis*-containing phytocannabinoids, which have been used in

epilepsy treatments for many years, have been demonstrated in studies [100]. This suggests that the endocannabinoid system directly or indirectly affects epileptogenesis.

CBD is the ligand of the endogenous receptor CB1 and reduces the symptoms of epilepsy with its anticonvulsant effect. During an epileptic seizure, excess glutamate is released from neurons; as a result, the endocannabinoid ligand CBD regulates the reduction of Ca^{2+} and Na^{+} ion flux by interacting with human T-type voltage-gated Ca^{2+} channels, inhibiting intrasynaptic reuptake of melastatin, TRPV receptors, and adenosine, and activating neuronal serotonin and glycine receptors [101–103]. Today, the drug Epidiolex, which is in the form of CBD oil, has shown positive results in children and young adult patients, but these studies are small-scale.

8.3 Antiemetic Effect

Nausea and vomiting are one of the side effects of cancer patients due to chemotherapies for treatment. This side effect significantly affects both the treatment and the lifestyle of the patient. CB1 receptors located in the dorsal vagal complex, which contains projections between the stomach and intestines and regulates vomiting; Cannabinoids have become important compounds for the abolition of the effects of chemotherapy induced vomiting and nausea [95].

Studies have shown that serotonin 5-HT3 receptor antagonists, neurokinin NK1 receptor antagonists, corticosteroids, dopamine antagonists, benzodiazepines, cannabinoids (THC and CBD components) and olanzapine have antiemetic (anti-vomiting) effects [52]. Currently, FDA-approved single-molecule cannabinoids dronabinol and nabilone are used as anti-nausea in cancer patients [95]. Although CBD has been found to reduce nicotine, lithium, and cisplatin-induced vomiting and nausea via the 5-HT1A receptor [104], since *cannabis* use has not been compared with other anti-emetic and anti-nausea drugs, priority shifts to other antiemetic drugs.

8.4 Antidepressant and Anxiolytic Effect

CB1 receptors, which are densely located in the prefrontal cortex, amygdala and hippocampus regions of the brain, affect the mechanisms that play a role in affective disorders and the elimination of psychotic effects. Phytocannobinoids and other compounds that exert their antidepressant, anxiolytic and analgesic effects via the endocannabinoid system or the 5-HT1A receptor; It may be a

potential treatment avenue for depression, anxiety, post-traumatic stress disorder, pain-induced insomnia, and neurodegenerative diseases [35].

Hemp helps to reduce the effects of anxiety, insomnia and nightmares that occur in post-traumatic stress disorder. In vivo studies have indicated that the endogenous receptor CB1 may be associated with the formation and extinction of fear [105]. Although there is limited evidence about its effects on anxiety, insomnia and depression until now, epidemiological results have indicated that *cannabis* has a reducing effect on anxiety.

The endocannabinoid system, which plays a role in the regulation of anxiety and mood, exerts its effects through endocannabinoid receptors located in the brain's medial prefrontal cortex, amygdaloid complex, bed nucleus of the tria terminalis, and hippocampus [106]. GABAergic and glutamatergic transmission by activation of the CB1 receptor [107] regulates the hypothalamic-pituitary-adrenal (HPA) axis, immune system activation, and neuroplastic mechanisms. This system also shows anxiolytic and antidepressant effects as a result of activation of 5-HT1A receptor and CB1 receptors with CBD and THC phytocannabinoids [108].

It has been shown that *cannabis* is linked to schizophrenia-causing alleles, and certain genes in early age *cannabis* use play a key role in regulating schizophrenia [109]. The THC psychoactive substance in *cannabis* increases the psychotic effects in schizophrenia, so the effects of CBD rather than THC in schizophrenia have been examined. CBD reduced the psychotic effects of both schizophrenia and THC [35].

Parkinson's disease, a neurodegenerative disorder, is the second most common disease. This disease causes muscle stiffness as a result of the loss of melanin-containing dopaminergy neurons in the substantia nigra pars compacta (SNpc), resulting in tremors at rest, slow motion, and deterioration in gait and posture. In studies, it has been found that activation of the endocannabinoid receptor CB2R increases microglial and astrocyte deactivation in certain regions of the brain, ensures the survival of neuronal cells by rearranging neuronal function, and also inhibits neuroinflammation by regulating functional deficiencies [81].

While attention deficit hyperactivation disorder (ADHD) and bipolar disorder are thought to have potential for disturbance of the endocannabinoid system, studies on this topic have not been conducted [35].

Depressive effects are increased in individuals using high doses of recreational *cannabis* [110]. Therefore, when recommending *cannabis*-based

drugs to people with depressive moods, special attention should be paid to not containing high doses of THC, which has a psychoactive effect.

8.5 Orexigenic Effect

It has been found that dronabinol, a *cannabis* product, has been shown to increase appetite, albeit slightly, in eating disorders and loss of appetite in HIV and cancer patients [29]. In studies, it was found that as the dose increased, the appetite-enhancing effect was also positively affected, but the effect of *cannabis* was less than the drug currently used in cancer-related anorexia [7].

8.6 Antispasmodic Effect

In a study to improve involuntary tics in patients with Tourette's syndrome, it was found that *cannabis* use reduces tics by more than 50% [9].

8.7 Antitumor Effect

Endocannabinoid receptor agonists can inhibit tumor formation and progression by influencing cancer cell migration, invasion and metastasis to other tissues and exhibit anti-prolative, anti-invasive and antiangionic properties, and can induce apoptotic death in cancer cells by autophagy. Linked between ECS and cancer is cyclic adenosine monophosphate (cAMP), mitogen-activated protein kinase (MAPK), protein kinase b (Akt), ceramide, reactive oxygen species (ROS), epidermal growth factor (EGFR) family, and cancer stem cells are well studied. In vitro and in vivo studies in cancer types such as breast, brain and colon have shown that CBD has anti-tumor properties [7].

9. Application Ways

The duration of action of cannabinoids taken into the body varies according to the route of administration, dose and drug interactions [35]. Exogenous cannabinoids are generally taken into the body by inhalation and oral route by smoking or vaporization for recreational or therapeutic purposes [40,102]. Although several studies have used various routes of administration such as eye drops, rectal route, sublingual route, their practical use is not very important [6]. These application methods determine the effects of the psychoactive substances in *cannabis* on the body.

When used by inhalation as a cigarette, the THC component quickly passes from the lungs to the blood and shows its psychoactive effect more

quickly. When THC is taken into the body, it is metabolized in the liver to the stronger psychoactive substance 11-OH-THC and the non-psychoactive 11-nor-9-carboxy-THC [111]. This is very rapid and these components act as markers in urine tests to detect *cannabis* use [112]. In addition, this way is therapeutic in eliminating short-term effects. On the way to evaporation, hemp shows its effect by affecting the central nervous system within seconds. In addition, it shows the same effects as smoking, and in this method, carcinogenic products formed as a result of combustion in cigarettes do not occur [6]. The vaping route has been proven to reduce neuropathic pain in clinical studies [40]. *Cannabis* begins to act within a few minutes after inhalation and reaches its peak at the end of 60 minutes and is kept at a constant plasma level for up to a maximum of 5 hours [113]. The initial effect of oral intake is slower than the other two methods, but the duration of action is longer. The advantage of oral use over other routes is that it will be given at certain concentrations.

Drugs containing hemp are used in the treatment of some diseases, which are approved by the FDA (Food and Drug Administration). Nabiximols, containing equal proportions of THC and CBD, is an oromucosal spray used to reduce spasticity in multiple sclerosis [114]. Brachial plexus avulsion and mist have shown negative results in pain associated with other disorders, except for peripheral, neuropathic pain [115,116]. Dronabinol contains THC derived from *cannabis* resin in capsule form, which is used in MS-related neuropathic pain, chemotherapy-induced nausea, and as an appetite stimulant in AIDS patients [117]. Nabilon, on the other hand, is a synthetic THC molecule in capsule form used to reduce symptoms in AIDS patients, similar to dronabinol, and to reduce the effects of chemotherapy-induced nausea and vomiting [96].

10. Toxic Effect and Side Effects

Cannabis is a drug mostly used to improve the symptoms of treatment-resistant diseases. In vivo studies have shown that 20mg of THC is intoxicating and the lethal dose is higher than 15,000 mg in humans, therefore very high doses of *cannabis* are required for lethal effect [5,118]. Therapeutic *cannabis* use is safe because the risk of death is low [5].

Medicinal *cannabis* is not fatal at low doses, mild or moderate side effects occur due to the presence of cannabinoid receptors in other tissues [40,119]. Short-term and common side effects seen with the use of THC, the main psychoactive substance of the plant, are dizziness, nausea and vomiting, dry mouth, increased sense of taste, appetite, and fatigue [40,120]. Other adverse

effects include altered mood, short-term memory impairment, cognitive deficits and, rarely, psychosis [5]. In addition, although it causes tachycardia and myocardial infarction by accelerating the heartbeat, it reduces these effects in long-term use [121,122]. CBD has no intoxicating properties and can be tolerated at higher doses than THC [5]. Common side effects for CBD use are diarrhea, while other side effects include decreased appetite, vomiting, somnolence, fatigue, fever, and changes in liver values [123–125]. Night-time dosing of THC or low-dose co-administration with non-psychoactive CBD may reduce side effects [126,127].

Cannabis, which is used for long-term recreational purposes, has an addictive effect, and as a result of the sudden discontinuation of *cannabis*, side effects such as sleep problems, irritability, and depression that may negatively affect daily life may occur [7,128,129]. These effects may initiate *cannabis* use again [130]. Therefore, while it is recommended to reduce the use of THC-containing drugs and discontinue, abrupt discontinuation of non-addictive CBD does not cause side effects [128,131]. It is also thought that CBD reduces addiction and can be used as a therapeutic agent in *cannabis* addiction [132].

These side effects differ according to dose amount, method of administration, interactions with other drugs, and individual sensitivities [40]. People who have not used *cannabis* throughout their life, people with psychotic or heart diseases, pregnant women and children should be careful when administering drugs containing *cannabis*, as side effects will be more common [5,133].

11. Discussion

Medicinal cannabis is a medicinal plant that plays a role in the treatment of many diseases and has been used since ancient times [9]. In this review article, we investigated the therapeutic effects and pharmacological activity of medicinal cannabis. As a result of our literature review, it has been seen that medical cannabis is effective in chronic pain and cancer pain. It shows this effect through CB1, TRPV1 and TRPV2 receptors. It exerts its anticonvulsant effects on TRPV receptors, serotonin and glycine receptors, and its antiemetic effects on endocannabinoid receptors and 5-HT1A receptors in chemotherapy-induced nausea and vomiting. It exerts its antidepressant and anxiolytic effects through endocannabinoid receptors and 5-HT1A receptors, and also has an oroxygenic effect in HIV and cancer patients, and an antispasmodic effect in patients with Tourette's syndrome. In vivo and in vitro studies have shown that it has an anticarcinogenic effect.

In comparison between opioid treatment and treatment with medicinal cannabis; it has been reported that hyperalgesia and deaths due to overdose as a result of opioid use were not observed with medical cannabis treatment. However, it has been reported that THC triggers schizophrenia in depressed patients and heart attack in patients with cardiovascular disease due to its psychoactive properties.

12. Conclusion

Although Medicinal *cannabis* shows therapeutic effects by affecting the endocannabinoid system, it is a plant that is approached with suspicion due to the THC molecule it contains. Since some of the mechanisms of action of the diseases are not known, there has been a tendency to current drugs rather than medicinal *cannabis*. However, existing drugs are not sufficient in the treatment of some diseases and these drugs show more toxic and side effects compared to medicinal *cannabis*. This study highlighted the importance of medicinal *cannabis* and shed light on new research for drug discovery.

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CHAPTER XIV

BIOCHEMICAL APPROACH TO VERTEBRAL DISC DEGENERATION

Mehmet BERKÖZ

(PhD, Associate Professor Doctor),
Van Yuzuncu Yil University, Faculty of Pharmacy,
Department of Biochemistry, Van, TURKEY,
E-mail: mehmet_berkoz@yahoo.com
ORCID: 0000-0003-4219-8054

1. Introduction

Intervertebral disc degeneration is a leading cause of disability leading to low back pain. It was estimated in a recent "Global Burden of Disease" study that 83 million people suffered from low back pain (1). Other studies have found the direct cost estimate for the treatment of this disease to be around $39-$126 billion in the US alone (2,3). Disc degeneration has a profound impact on quality of life with aging 2. Previous reports have indicated symptomatic disc degeneration to affect almost 400 million people worldwide (1). This motivates further studies focused on the molecular mechanisms driving disc degeneration. Current treatment strategies are palliative, failing to slow down or cure the condition. A mechanistic understanding would allow for approaches that treat the root causes of disc degeneration.

Disc homeostasis is critical for normal disc function. With degenerative changes, this homeostasis is severely disrupted, as evident by remodeling of the extracellular matrix (ECM), cell death, and loss of disc hydration that leads to narrowing of the joint space. Alteration of disc height and mechanical properties also affects the functioning of surrounding spinal structures, muscles, and ligaments. Other aspects, such as occupational, social, or environmental could also contribute to the onset of disc degeneration. The resident cells of the disc lose their phenotype during disc degeneration, causing inflammation and targeting other signaling pathways through extracellular matrix (ECM)

binding integrin receptors. Genetic factors are also believed to be contributors towards the development of this disease by altering the ECM and reducing the production of sulphated glycosaminoglycans (sGAG). Stenosis is another form of disc degeneration in which the spine canal narrows from the very beginning and can be congenital. Both surgical and non-surgical treatments along with traditional ones are being performed but the reason for lapse or the reverse of the progression is still unknown. A variety of in vitro and in vivo models of disc degeneration have been studied and compared to evaluate promising therapeutics that target degeneration at the cellular, molecular, and bulk tissue mechanics levels. Growth factors, stem cells and gene therapy are among the recent developments towards the therapeutic approaches to treat disc degeneration. This project focuses on the isolation of NP cells from Bovine caudal discs to study the mechanobiology aspect of disc degeneration, with the goal of identifying potential ways to mitigate and slow down the progression of the disease.

2. Intervertebral Disc Structure and Function

The intervertebral disc (IVD) is a fibrocartilage tissue present in between the vertebrae of the spinal column. IVDs generally function to provide motion, weight bearing capacity, and flexibility to the spine. The NP is gelatinous, rich in collagen II extracellular matrix (ECM) and proteoglycans, forming the core of the discs. The AF region consist of alternating ±30 degree lamellar layers of dense collagen I in the outer most region and increasing collagen type II in the inner region. The AF provides resistance against multidirectional movement of the spine. The IVD is a large and mostly avascular tissue, which requires that nutrient transport and waste exchange occur through diffusion and movement induced fluid convection in the tissue. The CEPs are the primary site of nutrient transport to and from the discs. The cells within each of these tissues regulate the structure and composition of the disc, effective interaction amongst these cells leads to the normal functioning and maintains disc homeostasis (4).

3. Intervertebral Disc Degeneration

Intervertebral disc degeneration (IDD) is a condition characterized by the breakdown of the discs in the spinal column leading to reduction in disc height. This can be caused due to genetic inheritance, ageing, or faulty mechanical loading of discs. According to Liang (2022), IDD is a growing clinical problem

related to lower back pain and often requires surgeries or other traditional physical therapy treatments (5). Recent studies have shown that the extracellular matrix plays an important role in the disc degeneration process due to its connection with the mechanical properties of the intervertebral discs (IVD) and its regulation of resident cells.

With degeneration, the balance between anabolism and catabolism is hampered. This condition could be the result of genetic inheritance, aging, or faulty mechanical loading of disc cells. Overall, disc cells lose their phenotype in response to changes in the disc environment, leading to further alterations in the extracellular matrix (ECM). As IDD progresses, there is a notable decrease in the proteoglycan and collagen II content in the disc, resulting in NP cell hypoxia, dysfunctional mechanosensing of the discs and proteolysis of the ECMs. Many genes have been correlated with the disc degeneration process along with remodeling of the ECM (5).

The inner most cells of the disc, the nucleus pulposus (NP) cells, lose their phenotypic characteristics with degeneration, driving inflammation and changes in the extracellular matrix (ECM). Two transcription factors that are influenced by these changes are Nuclear Factor-kappa B (NF-κB) and Yes-associated protein (YAP) (6-9). Previous work has shown that the ECM component fibronectin activates YAP by increasing F-actin and altering the morphology of the NP cells from circular to more flattened in the diseased condition (10). Given that imbalance in ECM proteins is a driver of both mechanical and cellular dysfunction in the disc, it is of utmost importance to consider the homeostasis of ECM proteins. Dysregulation of the disc microenvironment leads to progressive ECM remodeling, along with impaired disc functionality (4).

4. Fibronectin in Disc Degeneration

Fibronectin is a large glycoprotein residing in granulation tissues, body fluids and extracellular matrices in the form of disulfide bond multimers (11). It weighs 450 kDa with specific binding domains for DNA, fibrin, and collagen. Several regions of the molecule have been identified to give rise to subunits having altered amino acid sequences owing to the differential splicing of mRNA (11). Fibronectin promotes cell adhesion through active Arginylglycylaspartic acid (RGDs) sequences, allowing for clot stabilization and wound healing and almost all cell types have been shown to synthesize fibronectin in vitro (12,13). The N-terminus of fibronectin is believed to have a significant role in cartilage degeneration, and fibronectin fragments are also present in degenerating human

intervertebral discs (14). Fibronectin allows cells to organize the extracellular matrix through direct binding of integrins. The elevated synthesis of fibronectin in degenerated discs might suggest a response of cells to an altered environment like changes that occur in osteoarthritis (15). Enzymes like cathepsins can cleave fibronectin into)bioactive fragments, potentially providing a physiologic role in disc degeneration. Anderson et al studied the injection of a fibronectin fragment into a rabbit disc by microinjection and found progressive degeneration with high degree of reproducibility was observed (14). This indicates that fibronectin may be a critical driver and contributor to disc degeneration.

Fibronectin fragments (Fn-fs) have long been associated with Osteoarthritis (OA), leading to the degradation of biomechanical properties of the cartilage (16). Increased levels of fibronectin fragments have been associated with the synovial fluid of OA patients which in turn stimulate various inflammatory cytokines (17). Studies have found elevated levels of 110-140kDa C-terminal heparin binding Fn-fs, 29 kDa N-terminal heparin binding Fn-fs and 50kDa N-terminal gelatin binding Fn-fs in injured bovine cartilage when compared to that of the control group (18). In all these scenarios, Fn-fs regulate a positive feedback loop and act as pro-inflammatory mediators to induce cytokine expression to degrade the cartilage (19-21). They are responsible for modulating ADAMTS expression and signaling and induce MMP expression. Other studies have found Fn-fs induced stimulation of chondrocyte cytokine expression to be related to NF-κB activity for progressive ECM and matrix degradation, leading to cartilage destruction (22). The catabolism of the cartilage induced by Fn-fs has also been attributed to TLR-2 signaling pathway, but modification of the latter might prove therapeutic for cartilage destruction in OA (23).

Fibronectin plays an important role in the progression of cardiovascular diseases (CVDs) like heart failure, atherosclerosis, asthma and induce various other inflammatory signaling pathways. Immunohistochemistry and ELISA have confirmed aldehyde modified FN in atherosclerotic plaques due to the oxidation of LDL in vitro that leads to autoimmune response by promoting inflammation (24). Cellular FN has been a marker for vascular injury in asthma leading to vascular dysfunction with severe inflammation and prothrombotic blood alteration (25). Additionally, aging has been considered a prominent risk factor for CVDs attributing to the gain of function in IsoDGR motifs leading to atherosclerotic pathology. IsoDGR modified FN has been elevated in coronary artery diseases that activates macrophage via integrin receptor signaling and elicit inflammatory cytokines and chemokines (26). Another study showed

increased levels of FN containing extra domain A (EDA-FN) in patients of coronary artery disease based on computed tomographic coronary angiography thus, proving as a potential diagnostic step towards the disease (27).

5. Integrin Types and Their Ligands in the Intervertebral Disc

Integrins are a class of transmembrane heterodimers which consist of distinct α and β subunits. Integrin activation and ligand recognition are highly conserved in mammals and the RGD binding motif in fibronectin is recognized by several integrins, providing a mechanical connection between the cell and the extracellular matrix (ECM). Divalent cations like Ca^{2+} and Mg^{2+} influence the ligand binding specificity of integrins and allows them to be grouped based on the specific ECM molecules they bind. The binding of an integrin to an extracellular ligand activates several intracellular signaling pathways to regulate cell function. The cytoplasmic domain of the integrin is connected to the cytoskeleton via linker proteins like Talin, Vinculin and Ezrin/Radixin/Moesin (ERM) actin binding proteins (28). Integrins function as mediators between cytoskeleton and ECM, allowing cells to mechanically engage with their surroundings.

The interaction between cells and the ECM in the IVD of humans is integrin-mediated, regulating biosynthesis and cell attachment (29). With ageing, the phenotypic characteristics of the NP cells are lost, coincident with alterations cell-ECM interaction. Generally, NP cells are found to express β1, α3 and α5 integrins and blocking of β1 integrin has been shown to impede the attachment of cells to its specific ECM substrates (10). Additionally, the simultaneous blocking of α1, α2, α3 and α5 subunits completely inhibited NP cell attachment with laminin (29). A study by Speer et al. (10) showed that the blocking of α3 subunit could lead to the poor cell attachment to laminin along with a decrease in the cytoskeletal organization, reduced biosynthesis and altered expression of phenotypic markers (10). Thus, this study suggests that the integrin α3 mediated interaction has a large impact on the NP cell's ability to sense and alter their phenotype in response to laminin, and can slow NP cell driven degenerative changes in the disc. In the case of herniated discs, elevated expression of α5 and β1 subunits has been observed specifically in the extruded discs, but there was no significant difference in the expression of other α and β subunits (30). The first available data, in fact showed little to no variation in the integrin expression among the tissue section of the IVD (31). The β2

subunit is found as counter-receptors in white blood cells to fight infections and promote cell-cell interactions. However, in some cases they are seen to enhance cell-ECM interactions by mediating cytoskeletal organization and modulate cell signaling (32).

6. NF-κB, p65, and Inflammatory Signaling

NF-κB is a multifunctional transcriptional factor that consists of five subunits in the form of a p65/p50 dimer complex (33). Generally, it is inactive in the cytoplasm but upon stimulation by inflammatory factors, it translocates to the nucleus to regulate target gene transcription and expression. NF-κB is responsible for the regulation of the inflammatory cytokine response and catabolic matrix enzymes. NF-κB is also regulated by integrin signaling and mechanotransduction (34). As such, it is possible that inhibition of this pathway could reduce the inflammatory response by preventing cellular response to mechanical overloading and cell apoptosis (35,36). A study by Xu et al. (37) showed that the inhibition of NF-κB pathway promotes autophagy in intervertebral disc in rat nucleus pulposus (NP) cells (37). However, the relationship between the NF-κB pathway and apoptosis, inflammation, and autophagy is still unclear. Yi et al. (33) also observed that the inhibition of NF-κB decreases the expression of tumor necrosis factor (TNFα) and interleukin (IL-1β), downstream effectors of NF-κB. However, the mechanism of NF-κB inhibition protecting the NP cells from apoptosis is not clear. A study by Hwang et al. (38) showed p65 translocation to the nucleus in response to the inflammatory cytokine IL-1β, both in NP and AF cells (38). Because of the important role NF-κB plays in disc degeneration it provides a promising target for therapeutic approaches to slow or reverse the disease process.

7. YAP and Mechanosensing in the Disc

Another important transcription factor that is regulated by ECM interactions and mechanical forces is the YAP/TAZ pathway. They are considered as the switches for mechanosensing in the ECM composition and matrix mechanics (39). Focal adhesion (FA) formation forms the basis for actin cytoskeleton anchorage to integrin adhesions in the cell membrane, requiring integrins and other FA proteins. The YAP/TAZ pathway is known to regulate cell signaling by binding to transcriptional enhanced associate domain (TEAD) transcription factor, involving phosphorylation, thus confining YAP/TAZ into the cytosol,

restricting its ability to translocate to the nucleus (40). Once YAP/TAZ is inside the nucleus, it activates TEAD and induces expression of cell proliferation and apoptosis associated genes. The increase of F-actin and contractile forces allows the YAP/TAZ to function as a coactivator to bind with TEAD after translocating into the nucleus. The connections the actin cytoskeleton makes with the nucleus through the LINC complex have also been shown to be important regulators of YAP activation through deformation of nuclear pore complexes (8,41,42).

The formation of F-actin stress fibers promotes YAP activity. However, an increase in G- actin is insufficient to inhibit YAP activity. This indicates that while F-actin is important for activation of YAP, there are likely force sensitive actin binding proteins involved in driving the mechanical activation of YAP. Current research is focused on the molecular players involved in YAP mechanosensing and cytoskeletal dynamics, to identify the specific force sensitive proteins and protein domains that are involved (43).

8. Engineered Materials for Treatment of Disc Degeneration

NP replacement with engineered materials has gained much attention recently, with a large focus on injectable biomaterials (44-46). Important parameters for these materials are the mechanical properties of the implantable structures and their influence on the mechanics of the disc (47). Durability of the biomaterial and its ability to maintain physical support over many loading cycles is of particular importance. These materials should also not generate a systemic immune response that leads to aberrant remodeling (47). Hydrated synthetic polymers were among the first attempted strategies for in situ repair and mimic the hydrated properties of the healthy NP. However, control of polymeric swelling in vivo remains a challenge with recent attempts being made to re-design implant shapes to control its fragmentation upon swelling (48). Some other classes of polymers have been developed to undergo a transition from gel to solid in the NP niche (49-53). These also aim to induce minimal damage to the AF tissue to avoid NP extrusion leading to spinal impingement and associated disfunction. Hyaluronan-collagen or glycosaminoglycan containing polymers generate osmotic pressure to maintain disc mechanics and hydration as well as NP cell viability (47). Both the strategies mentioned above need rigorous clinical trials to study the interaction between cell-ECM and other local cell populations.

Another relevant area of study is that of biomaterial design for implants such as native cell carriers to maintain disc height and restore histologic

appearance for long durations after implantation (54,55). An important attribute is also biocompatibility with the endogenous cell population of the host (56). Studies have shown that fibrin gels containing TGF-β can preserve disc height by inhibiting apoptosis upon delivery with allogenic MSCs (57). Additionally, hydrogels with full length laminin have been developed to improve NP cell attachment with appropriate integrin signaling and gene expression, driving higher sGAG synthesis (58,59). It has been shown that NP cells prefer binding to laminin over collagen and fibronectin when healthy (29,60). On the other hand, RGD peptides have been found to increase AF cell attachment when conjugated with silk scaffolds (61). AF repair strategies have focused on tissue adhesives or fibrous scaffolds, as opposed to injectable material therapeutics. Aligned polymeric nanofibers like silk and collagen with a hydrogel are produced by electrospinning to mimic the structure of the AF tissue and restore mechanical function of the disc (62). Polymers such as PLA, PCL, silk or glycosaminoglycans are used in combination with biocompatible cross-linkers like genipin, fibrin or riboflavin for void filling. Design of AF patches can also help with the restoration of mechanical properties post repair (47,62). Overall, biomaterial design shows great promise to improve disc health through targeting of disease specific pathways. These could be used to enhance the survival and differentiation of resident cells and restore the structure and mechanical function of the disc (63).

9. Therapeutic Approaches for Managing Disc Inflammation and Degeneration

One of the confounding factors related to disc degeneration is that patients with a degenerate disc are often asymptomatic, without significant pain, which leads to the progression of undiagnosed IDD with age (64-67). The lack of pain makes it difficult to distinguish the reasons for the transition of painless disc degeneration to a pain associated disc (68). Signaling pathways like NF-κB, MAPK and toll like receptors (TLRs) play pivotal roles in the catabolism of ECM molecules and the production of inflammatory factors (69,70). To suppress inflammation, inhibitors like infliximab and atsttrin have been shown to reduce back pain in rats by targeting the receptors of TNF-α and decreasing inflammatory cytokine production (70,71). On the other hand, a single injection of IL-1Ra has shown therapeutic effect by decreasing the production of MMPs and ADAMTS4 which otherwise induces degradation of ECM and degenerate

histological grade (72). IL-1β is a proinflammatory cytokine responsible for driving inflammation during the progression of disc degeneration (73). Thus, deletion of IL-1Ra could result in accelerated degeneration and an increased histological grade of IDD (74). In vivo studies revealed IL-1Ra delivered by fluorescent labeled microspheres could inhibit the activity of IL-1β for a clinically relevant time, up to 28 days when compared to bolus injection alone, resulting in an increase in sGAG production for both NP and AF cells (75). This approach has gained popularity due to its significant impact on a variety of inflammation related diseases (76). TGF-β1 also regulates the ERK1/2 signaling pathway to inhibit specific target receptors such as TNFR1 – core mediator of TNF-α signal transduction and TNFR2 – regulating immune function in disc degeneration (76,77). However, TGF-β1 also activates a contractile phenotype and is a known regulator of fibrotic disease progression, so its use therapeutically is convoluted.

Clinical treatments employ bioactive agents that show promise for suppressing inflammation. Platelet rich plasma (PRP) contains a mix of growth factors like TGF-β and VEGF to exert a dampening effect on inflammation by promoting tissue regeneration (78,79). Other therapies include oral or injectable therapeutics delivered via absorption and diffusion in the avascular IVD, helping to slow or reduce its degradation (80). Several studies have reported drugs like melatonin, celastrol and glucosamine sulfate for the treatment of IDD by targeting specific cell surface receptors and downregulating matrix remodeling enzymes which in turn led to the increase in collagen II and aggrecan (81,82). However, these approaches are in their very early stages and are limited to only in vitro (83).

Since IDD is also associated with loss of viable cells, cell replacement therapies could mitigate IDD and prove useful as a potential regenerative approach. Fibroblasts, bone marrow derived cells or disc derived chondrocytes have all been implicated as possible candidates for cell replacement therapies (84-86). A recent shift has been to a focus on stem cells derived from bone marrow, but they lack stability of integration into the NP (87). However, this is the only genre which has claimed cells to differentiate into chondrocyte lines and confirm the presence of cells post transplantation over a long period (88).

10. Conclusions and Perspectives

A thorough understanding of the underlying mechanism behind IDD at the molecular, biochemical, cellular, and tissue/ECM levels, will contribute to

innovative and more targeted strategies to slow down disc degeneration. As alternatives to traditional surgical based treatments, research on regenerative therapies and medicines show promise in restoring NP cells and repairing or regenerating the degraded matrix. Since low back pain is still a poorly diagnosed disease, the increase in economic burden among the large population that isn't diagnosed until advanced degeneration is present, would still be problematic. New methods for early detection in combination with regenerative approaches would lower the cost of treatment by providing methods to diagnose and reverse degeneration to alleviate the adverse effects observed with disease progression.

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CHAPTER XV

STUTTERING, INTELLIGENCE AND MUSIC

Ayşe Sanem ŞAHLI

(Prof.Dr.), Hearing and Speech Training Center, Vocational School of Health Services, Hacettepe University, Ankara/Türkiye
E-mail: ssahli@hacettepe.edu.tr
ORCID: 0000-0001-5050-8994

1. Introduction

Stuttering is one of the common speech disorders in society. Stuttering, which occurs for various reasons, affects the individual differently. In this section, the relationship between stuttering, intelligence and music will be discussed.

2. Stuttering

Stuttering, defined as the irregularity of speech rhythm and fluency by pauses, is one of the most complicated speech disorders of which the unknown aspects are the most [1-3]. Stuttering is explained as a disorder in the speech rhythm by which the person knows exactly what to say, but cannot say because of involuntary repetition, prolongation, or pauses in the sounds. One of the most common symptoms of stuttering is the repetition of the words, sentences and/or syllables [4-6]. Also, some researchers describe stuttering in terms of: (a) the observable characteristics of the speech difficulty (impairment), (b) the functional communication difficulties experienced in the speaker's everyday life (disability), and (c) the impact of the stuttering disorder on the speaker's overall quality of life (handicap) [7,8].

Stuttering is a speech disorder which is seen in all cultures, adversely affects approximately 1% of the population (68 million people worldwide) and 5% of children having a stutter, is unwanted and varies Its prevalence varies in

all cultures and ethnic groups [9,10]. In a study conducted in the US and Europe, the proportion of stutterers in the society was found to be 0.7%, and the ratio of girls/boys varied between 1/3-1/5 [11]. Also, American Speech Language and Hearing Association (ASHA) and some researches indicates that stuttering incidence reaches a cumulative rate of 8.5% by 3 years of age and 11% by 4 years of age [12-14]. Stuttering is seen in males more than females. Even though the male to female ratio in stuttering has been differently indicated in each study, almost every study verified that the stuttering is more common among males [15-18].

Numerous studies have sought to identify differences between people who stutter and people who do not stutter. In many cases, this research has revealed that people who stutter are very similar to people who not stutter in terms of characteristics such as XYZ. One characteristic that has shown mixed results is intelligence.

3. Stuttering and Intelligence

Intelligence is the sum of various mental abilities, such as abstract thinking, comprehension, problem-solving, applying knowledge to new situations, reasoning, memory, and the use of knowledge gained from past experiences [19]. Although there are international studies that have been carried out to analyze the relationship between stuttering and intelligence, the number of scientific studies that analyze this subject in our country is scarcely any. Whereas in some studies carried out on stuttering and intelligence, it has been stated that there is no difference between stuttering and non-stuttering individuals in terms of intelligence, and in some studies, it has been emphasized that the average intelligence scores of stuttering children are much higher than fluent speaking children and in some of the studies it has been determined lower [20-25].

Some studies on stuttering and intelligence have found no difference between stuttering and non-stuttering individuals (citations), though others have found that the average intelligence scores of children who stutter are higher (citations) or lower (citations) than nonstuttering children. Some references have also indicated that the prevalence stuttering among intellectually impaired individuals appears to be far higher than in the general population. Also, some references indicate that the stuttering among mentally-retarded individuals appears to be far higher than the general population [26].

Stuttering is a communication disorder that can significantly impact many aspects of an individual’s life. According to researchers, the most distinctive

aspect of stuttering is the production of speech by disrupting its fluency in different ways such as repetition of word parts, prolongation and blocks. Specific strategies implemented in stuttering therapy include desensitization to stuttering, cognitive restructuring, self-acceptance, purposeful self-explanation, and a combination of fluency development and stuttering modification approaches [27]

Many children who stutter are exposed to negative emotional and cognitive experiences as a result of their communication difficulties. Stuttering can often be accompanied by low self-esteem and decreased self-confidence and other negative effects, and these factors can negatively affect the child's overall communication ability. As the disorder progresses, negative reactions can become a significant problem, especially for some children who stutter. Apart from this, the negative reactions of the people around the child can also play an important role in the child's stuttering experiences. These negative experiences not only have a negative impact on the child's ability to communicate; They can also hinder advances in therapy. Therapy aims to create some behavioral changes in children or to gain new behaviors in social, emotional and cognitive areas, especially speech. During this process, it is very important to enable children to learn by identifying their strengths and weaknesses, to develop their superiorities with different methods, and to support other areas of intelligence [7].

According to Gardner, intelligence is not a single IQ number, but a mosaic of abilities located in different parts of the brain. At the same time; It gives the individual the opportunity to solve the problems he encounters in real life. Also, Gardner say every person has the ability to increase and develop their own intelligence.

According to this understanding, no matter what age and intelligence level a person is, the capacity of human intelligence can be developed, changed and improved. Every human being has all the various areas of intelligence. Multiple Intelligence Theory does not mention the existence of a single intelligence in every person. Instead, he argues that every person has some ability in all areas of intelligence. For this reason, each person may be highly developed in some areas of intelligence, moderately developed in others, and very poorly developed in others. Every person can develop each of the various intelligence areas to a sufficient level. Contrary to the belief that an individual's inadequacy in any intelligence area is innate and cannot be changed, the Theory of Multiple Intelligences argues that each individual has the ability to develop at a very high level in all intelligence areas if adequate and appropriate support is provided [28].

According to Gardner, the types of intelligence that exist in different amounts in each individual and can be developed are; verbal/linguistic intelligence, logical/mathematical intelligence, visual–spatial intelligence, musical-rhythmic intelligence, bodily/kinesthetic intelligence, interpersonal-social intelligence and intrapersonal intelligence.

-**Verbal–linguistic intelligence** involves sensitivity to spoken and written language, the ability to learn languages, and the capacity to use language to accomplish certain goals.

-**Logical–mathematical intelligence** consists of the capacity to analyze problems logically, carry out mathematical operations, and investigate issues scientifically.

-**Visual–spatial intelligence** involves the potential to recognize and use the patterns of wide space and more confined areas.

-**Musical–rhythmic intelligence** involves skill in the performance, composition, and appreciation of musical patterns. It encompasses the capacity to recognize and compose musical pitches, tones, and rhythms.

-**Bodily–kinesthetic intelligence** entails the potential of using one's whole body or parts of the body to solve problems. It is the ability to use mental abilities to coordinate bodily movements.

-**Interpersonal–social intelligence** is concerned with the capacity to understand the intentions, motivations and desires of other people. It allows people to work effectively with others.

-**Intrapersonal intelligence** entails the capacity to understand oneself, to appreciate one's feelings, fears and motivations [28,29].

The key concept of Gardner's Theory of Multiple Intelligences is the word "plural". Because intelligence is versatile. Intelligence, which is genetically inherited from birth, can be developed, changed, and being intelligent can be learned to a certain degree. The development of intelligence areas depends on the provision of appropriate environments and opportunities rather than natural developmental capacity. For this reason, Gardner emphasizes that children's capacities should be evaluated rather than focusing on what they can do now.

An important factor affecting intelligence development is the environment. The child needs an environment equipped with rich stimulants in order to use his innate mental potential and develop his abilities. The goal can be achieved if teaching is done using methods suitable for each intelligence field. The most

successful way is to apply methods that are suitable for the type of intelligence that children have.

4. Stuttering and Music

Music is a part of the learning and development process from the womb. Music education has a positive impact on all areas of development of both normal and hearing loss children. In a study conducted on the subject, it was found that those who had not received regular music education before. A musical activities education program was applied to preschool children for six weeks and ıts effect on children has been investigated. As a result of the study, it was concluded that musical activities were giving children the opportunity to express themselves and ensuring their active participation. It has been observed that it enables the release of energy and improves listening and motor skills and social communication [30]. Musical events that children enjoy participating in It has significant effects on language development. Together we improve children's reading skills.

Music is a very important activity in child development. It improves the child's intelligence capacity and contributes to cognitive development. Music stimulates the brain and organizes bilaterally distributed attention. Different neural networks are accessed when verbal material is displayed through song; An alternative information processing pathway is used in the brain [31].

Music improves the child's intelligence capacity and contributes to his cognitive development. The child relaxes emotionally by expressing himself., gains social harmony by learning how to behave in society. Also, he/she earns to relax in a group and act with others without attracting attention and communicate effectively. Music therapy has provided an alternative treatment opportunity for many people with psychological problems ranging from depression and stress to physical problems, especially in the field of hearing and language-speech disorders. When the international literature is examined, a very limited number of studies examining the relationship between hearing, speech and language disorders and music therapy stand out. [32,33].

In our country, scientific research in this field is almost non-existent. It is seen that studies on music therapy mainly focus on psychological disorders. There are many similarities between speech and music; Many of these serve as suitable foundations for incorporating music into stuttering therapy. Studies show that an interaction exists between the syntactic processes of both music and language, with both likely relying on shared processing resources in the

brain. Neural mechanisms related to these processes can be altered by music [34,35].

When considering the types of treatments to use for individuals who stutter, it is important to consider which treatment will best benefit the cases and help improve overall quality of life. Music's neural pathways in the brain are more widespread; Therefore, involving the brain in music helps activate weaker areas in individuals who stutter. Music is powerful and has a strong impact on a person's emotional states, which in turn affect learning, attention, and executive function abilities.

Music therapy is a method used therapeutically in countries with developed health. From past to present, music therapy has been used in many environments such as kindergartens, schools, re/habilitation centers, hospitals, nursing homes, nursing homes, community centers and even at home. Music therapy, whose positive effects on individuals who stutter are supported by different studies, can be used both as an educational material and as an educational method, in supporting speech-language development, in improving interpersonal relations and social skills, and in gaining rhythm perception.

Music therapy is very advantageous for individuals who stutter because it frees them to express themselves and increases their self-esteem. It activates the brain regions required for motor control and fluency of speech and allows the individual/child to have fun while doing so. Additional research is certainly needed to continue exploring the usefulness and application of music therapy, but current findings specifically point to its potential to enrich children's experiences with speech and language, an important area of development in a person's life. [36].

An important study on the subject was conducted at Hacettepe University Vocational School of Health Services Hearing and Speech Training Center. Before the study, the training center management and employees were informed about the purpose, method and practices of the research and the necessary permissions were obtained. In addition, the children and families who participated in the study were given information about the research. and 'Voluntary Information and Consent Form' was signed. 10 children (5 girls, 5 boys) aged 4–8 years (Mean age: 6.4) with severe stuttering were included in the study. For each stuttering child participating in the study, after the 'General Information Form' was filled out through a mutual interview with the mother and/or father, the Teele Multiple Intelligence Inventory was applied to each child, and the results of the dominant intelligence area were recorded (before music therapy.) All of children were

evaluated by TIMI (Teele Inventory of Multiple Intelligences) after attending a music therapy program (3 months, 45 minutes/per week, a total of 12 sessions) again. Our study applied the concept of creative music therapy based on the Orff-Schulwerk approach. Both children and therapist/music teacher were active in singing and making music with Orff instruments (i.e. rhythm sticks, maracas, tringles, shakers, bells, drums, xylophones, glockenspiels) and a piano. The study results exposed that there was a statistically significant difference on verbal-linguistic intelligence (before music therapy X: 3.4, SD: 1.5 – after music therapy X: 5.1, SD: 1.3), logical-mathematical intelligence (before music therapy X: 4.5, SD: 1.2 – after music therapy X: 5.9, SD: 1.8) , musical-rhytmic intelligence (before music therapy X: 3.1 SD: 1.2 – after music therapy X: 4.8, SD: 1.4) and interpersonal-social intelligence (before music therapy X:3.0, SD: 1.6 – after music therapy X: 4.2, SD: 1.7) and averages of scores of these multiple intelligence types in stuttering children after music therapy program ($p<0.05$) [37].

In another study on stuttering and music therapy, the effect of music on the social skills of children who stutter was investigated. The study includes parents (mother/father) of 10 stuttering children (5 girls and 5 boys) who ranged in age from 7-12 years. These stuttering children participated in music therapy programs for 4 months (45 minutes/per week, a total of 17 sessions). There are six music activities in a music therapy season; listening to sounds and music, rhythm, singing, dramatization with music, creative dance and story with music. The social skills performances of children were evaluated by Social Skills Evaluation Scale (SSES) before music therapy and after music therapy. SSES includes 69 items and seven subdomains; Basic social skills, interaction skills, starting and maintaining relationship skills, group skills, emotional skills, speech skills and cognitive skills. When the results were examined, there seemed to be significant difference statistically in total score of SSES (before music therapy X: 146.9, SD: 27.452 – after music therapy X: 159.8, SD: 46,163),basic social skills (before music therapy X: 34.90, SD: 8.412 – music therapy X: 40.30, SD:10.698),emotional skills (before music therapy X: 13.80, SD: 3.938- after music therapy X: 16.00 SD: 5.249) and interaction skills(before music therapy X: 36.30 SD: 8.459- after music therapy X: 39.90, SD: 13.819).. These results emphasize that music has positive effects on the social skills of children who stutter [38].

The emotional effects of stuttering on children alone are very much devastating on his or her emotional health. Not only has that, stuttering

unfavourably affected not just a child's social skills but his or her communication skills as well. Because of stuttering, many kids think that making friends and building relationships become very disappointing and sometimes traumatizing [39]. Music can greatly help a lot to lessen the emotional effects and socialize with others. Music therapy can be used as an educational method for supporting of abilities of speech- language, social and all the development areas in stuttering children. Music therapy from a neuropsychological point of view may support human communication skills that are organized rhythmically in accordance with neurological processes. Thus, active, creative music therapy works immediately with the contact and communication between the improvising participants. In such a setting, the integration of several senses, like hearing or seeing, motor abilities, and emotion, is of vital importance, because both verbal communication and joint musical improvisation require a meaningful integration of these senses. Thus, music therapy may offer a specific space to test and develop various senses on a level appropriate to the child's individual abilities and speed. Therefore, music therapy may provide a very fundamental, basic, and supportive therapy for children with stuttering [40,41].

5. Conclusion

Stuttering is a communication disorder that can significantly impact many aspects of an individual's life. According to researchers, the most distinctive aspect of stuttering is the production of speech by disrupting its fluency in different ways such as repetition of word parts, prolongation and blocks. Intelligence assessments are extremely important in individuals who stutter, especially in children. Multiple intelligence assessments are especially useful in determining the stuttering child's strengths and weaknesses and determining the most successful therapy method. Specific strategies implemented in stuttering therapy include desensitization to stuttering, cognitive restructuring, self-acceptance, purposeful self-explanation, and a combination of fluency development and stuttering modification approaches. Music is a very useful 'education material' and a very effective 'education method'. Music therapy supports mental, physical, speech-language and social-emotional development of children addition to artistic development. The use of music therapy in children who stutter plays an active role in the development of verbal-language skills, interpersonal communication, social skills, logic-mathematics and musical rhythmic skills.

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CHAPTER XVI

DELIRIUM AND NURSING CARE IN ORTHOPEDIC SURGERY

Tülin YILDIZ[1] & Çağla AVCU[2]

[1](Prof. Dr.), Faculty of Health Sciences,
Department of Nursing, Tekirdag Namık Kemal University,
E-mail: tyildiz@nku.edu.tr
ORCID:0000-0002-4981-6671

[2](Research Assistant), Faculty of Health Sciences, Department of Nursing, Tekirdag Namık Kemal University,
E-mail: caglaavcu@nku.edu.tr
ORCID: 0000-0002-7786-2288

1. Introduction

Orthopedic surgeries are performed to treat diseases and injuries related to the musculoskeletal system, correct deformities and provide surgical repair. (1) Among these surgeries, knee and hip arthroplasty are the most common surgeries. (2) Hip fracture is a significant cause of morbidity and mortality, especially in geriatric patients. It is estimated that hip fractures and hip arthroplasty surgeries will increase with the increase in the number of individuals in the geriatric age group. (3)

Despite advances in surgery, the risk of complications is high after orthopedic surgery, especially in geriatric patients. Among these complications, delirium is the most common. Delirium is diagnosed in approximately 4.5-41.2% of orthopedic surgery patients. (4) Delirium prolongs recovery and hospital stay in orthopedic surgery patients and increases morbidity and mortality. (5)

Nursing care plays an important role in determining delirium risk factors, diagnosing and preventing delirium in orthopedic surgery patients. (6, 7)

2. Delirium

Delirium is a syndrome characterized by acute onset and rapidly developing cerebral dysfunction with fluctuations in cognitive functions, affecting attention, memory, thinking, sleep-wake cycle and level of consciousness. (8)

This syndrome is classified into three subheadings: hypoactive, hyperactive and mixed delirium. Hypoactive delirium is characterized by decreased motor activity, apathy, decreased awareness and speech, decreased alertness, and tired appearance. Behaviors such as hyperactive delirium agitation, restlessness, irritability, rapid speech, loud talking and laughing, hallucinations, increased motor activity, and harming oneself or others are observed. Mixed delirium is the condition in which both hyperactive and hypoactive delirium features occur for short periods of time. (9, 10)

Although the pathophysiology of delirium is not clearly known, it is estimated that it occurs as a result of many factors and risk factors and has a complex mechanism. Changes in neurotransmitters such as serotonin, acetylcholine and dopamine can lead to an increase in the level of cytokines, disruption of the blood-brain barrier and an inflammatory response that affects cerebral oxidative metabolism, causing delirium. (8)

Risk factors that lead to the development of delirium can be examined in two groups: predisposing and precipitating. Predisposing factors are risks that are present at the time of admission to the hospital and increase the tendency to develop delirium. These risk factors include patients' gender, age, comorbidities such as cognitive problems, dementia, vision problems, polypharmacy, depression, and chronic diseases. Precipitating factors are risks that trigger and accelerate the development of delirium. They differ from predisposing factors in that they usually begin with hospitalization and are potentially modifiable. These risk factors include medications (such as analgesics, anesthetics), fluid electrolyte imbalances, catheter use (such as urinary catheter, central catheter, nasogastric catheter), bleeding, intubation time, surgical practices (such as waiting time for surgery, duration and type of surgery), There are factors such as disruption of circadian rhythm and length of stay in the intensive care unit. (11-13)

Delirium is most commonly seen in patients in surgical clinics after intensive care units. However, delirium is seen more frequently in patients in the geriatric age group and in patients who have undergone heart and hip surgery compared to other patient groups. It is estimated that delirium occurs

in 50% of hospitalized geriatric patients, 3-53% of patients undergoing major surgery, and 83% of patients in intensive care. (11) In the postoperative period, delirium usually occurs within 24-72 hours. (14) Stress factors such as physical weakness, decrease in cognitive functions, environmental change, acute illness and surgery facilitate the formation and increase of the severity of delirium. (15)

With the development of postoperative delirium, patients' hospital stay is prolonged, their cognitive and physical conditions deteriorate, the need for long-term care and dependency increases, and their quality of life decreases. Additionally, hospital readmission, healthcare costs, morbidity, and mortality rates are also increasing. It is estimated that the mortality rate increases by approximately 25% due to delayed diagnosis and treatment. (14-16)

Risk factors of delirium need to be identified, prevented or treated by early diagnosis. (11, 13)

3. Orthopedic Surgery and Nursing Care in Delirium

Orthopedic surgeries are generally among the long-lasting surgeries and can be traumatic for patients and cause an increase in surgical stress response. Orthopedic surgeries are a risk factor for the development of delirium. Neurotransmission, inflammation, and surgical stress are predicted to cause delirium in orthopedic surgeries. The combination of surgical stress with pain and inflammation leads to a systemic inflammatory response. Cytokines such as interleukins, tumor necrosis factor and interferons are secreted at the time of cellular damage and repair and play a role in the inflammatory process. As a result of this inflammatory response, the permeability of the blood-brain barrier increases, causing an increase in neurotransmitter and cytokine release. However, in geriatric patients, the decrease in the number of brain cells, cerebral blood flow and nerve conduction velocity with aging affects brain functions. This situation increases the risk of delirium in geriatric patients in orthopedic surgeries. (17, 18)

In orthopedic surgeries, the development of delirium after surgery negatively affects patients in the short and long term. In addition to increasing complications related to the surgical field, it can lead to longer hospital stays and recovery times, increased addiction and hospital readmission rates, increased falls and pressure ulcers, and permanent cognitive damage such as depression, memory and abstract thinking problems. Additionally, morbidity and mortality are increasing. (18)

It is estimated that up to 40% of the incidence of delirium after surgery is preventable. The patient's care should be planned multidisciplinary. In this collaboration, nurses play an active role in the care of patients before, during and after surgery. It is important to prevent delirium rather than treat it. Nursing care includes practices such as assessing cognitive activity and orientation, preventing dehydration and constipation, pain management, hypoxia and infection monitoring, early mobilization, reducing polypharmacy, monitoring sleep and sensory stimuli, supporting fluid and nutritional intake, ensuring family participation in care, and environmental regulation. (1, 6, 19)

Facilitating families' participation in care and visits, and providing orientation with environmental stimuli such as clocks and calendars may be effective in preventing delirium after orthopedic surgery. Identifying and accurately assessing cognitive activity is an important first step. Many scales are used to evaluate cognitive activity and orientation. Cognitive assessment and recording by nurses daily and at each shift change can make it easier to recognize the signs and symptoms occurring in the patient. At this point, "Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)" and "Intensive Care Delirium Screening Checklist (ICDSC)" are frequently used for the early diagnosis of postoperative delirium. "Neelon and Champagne Confusion Scale (NEECHAM)", "Richmond Agitation and Sedation Scale" and "Nursing Delirium Monitoring Scale-Nu-DESC" are used to evaluate the mental status of patients. Apart from these scales, "Delirium Rating Scale (DRS)", "Delirium Observational Screening Scale (DOS)" and "Family Confusion Assessment Method (FAM-CAM)" can also be used. (13, 19, 20)

The PRISME approach is recommended as a method to evaluate risk factors when delirium is suspected. With the PRISME approach, nurses can identify modifiable risk factors to prevent the development of delirium in the patient. This approach includes Pain and Poor nutrition (P), Retention and Restraints (R), Infection and Immobility (I), Sleep disturbances and Sensory deficits (S), Metabolic imbalance, Mental status, Medications, (M), Environmental changes (E). (19)

In addition to these assessment tools, several studies have reported positive results using the "4AT," a rapid screening tool for delirium. 4 The AT is a brief, easy-to-use, validated tool for diagnosing the presence of moderate to severe cognitive impairment or delirium and requires minimal training in its use. It can be used as both an initial screening and daily assessment tool to monitor delirium and includes evaluation of patients with severe stupor or agitation. The

tool consists of four sections that are scored and then collected. In these sections, alertness, attention, acute change in cognition and orientation are scored using AMT4 (Abbreviated Mental Test-4). (19)

Dehydration, constipation, and infection can facilitate delirium. Fluid electrolyte balance should be monitored, fluid intake and easy availability of fluids to the patient should be supported, bowel and bladder emptying should be monitored, bowel cleansing should be performed if necessary, signs and symptoms of infection should be observed, and risk-reducing methods (such as removing the urinary catheter) should be applied to prevent infection. (19)

The patient's pain should be evaluated, pharmacological and non-pharmacological methods should be applied for pain management, and the effectiveness of these methods should be monitored. (15, 19, 21, 23)

To prevent hypoxia, oxygen saturation level should be monitored and oxygen therapy should be applied when necessary. (15, 19, 21, 23)

Patients should be encouraged for early mobilization after surgery, their participation in daily living activities should be supported, they should have access to auxiliary equipment that can be used during mobilization, and no restrictions should be applied. (15, 19, 21, 23)

Antipsychotics and benzodiazepines are generally used in the pharmacological treatment of delirium. The effectiveness of these drugs should be monitored and information should be given to avoid taking drugs that affect the central nervous system. (15, 19, 21, 23)

Sleep problems can lead to delirium. Environmental stimuli such as noise and light should be reduced, treatment and care practices should be planned according to sleep hours, adequate lighting should be provided during the day to ensure the sleep-wake cycle, methods such as drinking hot drinks before sleep should be applied, and pharmacological methods should not be used routinely for sleep problems. (15, 19, 21, 23)

Patients should be observed for nutritional deficiency. They should be supported in terms of fluid and nutrition, oral health and swallowing status should be monitored, and oral care should be given. (15, 19, 21, 23)

Hospitals are an environment where patients go beyond their routine and are unfamiliar with it. Arrangements should be made to reduce patients' stress and remind them of the environment in which they live in terms of sensory stimuli and environmental factors. A therapeutic environment should be created in terms of lighting, noise and temperature. At the same time, patients should be provided with access to equipment such as glasses and hearing aids. Nurses

should pay attention to communication with the patient. Orientation should be supported by hanging a table in the room where the patient is located and providing information such as where the patient is, day and date, room number and the names of the healthcare professionals providing care. Patient orientation in terms of person, place and time should be provided every day. The patient's family and relatives should be encouraged to visit and participate in care. The importance of these visits should be explained to the patients' families and relatives in order to create a sense of familiarity for the patients. Both patients and their families should be supported regarding their fears and concerns. (15, 18, 19, 21-23)

4. Conclusion

Delirium is among the most common complications in orthopedic surgeries. Hospital stay and recovery time, hospital readmission rates, addiction status, and morbidity and mortality rates increase due to delirium. Delirium is easier to prevent than to treat. Nurses play a key role in the care of patients and can notice changes in the patient before other health professionals. At this point, after orthopedic surgery, delirium can be prevented with nursing care in terms of cognitive activity, orientation, dehydration, constipation, pain, hypoxia, infection, mobilization, medications, sleep, sensory stimuli, fluid and nutritional intake, family participation and environmental regulation.

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CHAPTER XVII

BALANCE AND POSTURAL CONTROL

Gülfem Ezgi ÖZALTIN[1] &
Dilan DEMİRTAŞ KARAOBA[2] & Havva ADLI[3]

[1](Dr.Research Asist.), Inonu University, Faculty of Health Sciences,
Department of Physiotheraphy and Rehabilitation,
E-mail: gulfemezgi.ozaltin@inonu.edu.tr
ORCID: 0000-0003-1591-4844

[2](Ph.D), Inonu University, Faculty of Health Sciences,
Department of Physiotheraphy and Rehabilitation
E-mail: dilandemirtas92@gmail.com
ORCID: 0000-0002-6754-9335

[3](Ph.D Cand.), Vocational School of Health Services,
Department of Therapy and Rehabilitation
E-mail: havva.adli@inonu.edu.tr
ORCID: 0000-0002-4802-9131

1. Introduction

The terms balance and postural control are often used interchangeably in the human body. Equilibrium is defined mechanically as the situation in which the resultant of the forces acting on the object meet each other. In the human body, it means trying to remain stable without moving the body's center of gravity beyond the support surface. (1) Balance is examined under two subheadings: dynamic and static. Static balance is related to the center of gravity and the boundaries of the support area. Dynamic balance is the ability to maintain movement while a person is in motion. Postural control is the ability to protect the center of gravity within the limits of stability against stimuli from the external environment and to develop postural adaptation against this. Postural control requires both postural orientation and stabilization. Maintaining balance

depends on three important conditions: maintaining movement, ensuring a smooth transition from one voluntary movement to another, and maintaining the body's position against external stimuli. (2) Since postural control arises from the body's relationship with the external environment, it is not considered a single system. It can be considered as an interaction of multiple sensorimotor processes. It requires the integration of sensorimotor strategies in the central nervous system using information from the visual, vestibular and somatosensory systems (Figure 1). (3)

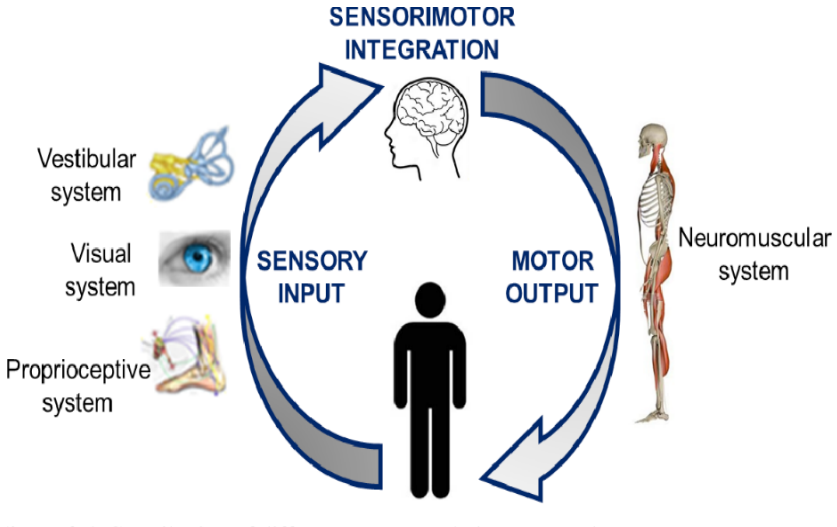

Figure 1. Postural Control

Balance disorder may be due to many factors. To better understand this, the systems that contribute to postural control need to be evaluated more comprehensively. For example, an individual who has had a stroke experiences balance problems because they cannot use the somatosensory system well, while an individual with vestibular involvement experiences a loss of balance because their vestibular reflexes do not work properly. Strategies developed for postural control in the body can be both "proactive" and "reactive". Proactive strategy is the maintenance of balance in the face of a predictable situation, while reactive strategy requires the necessary movement strategy or muscle activity to maintain continuity of postural control in the face of an unpredictable situation. Ankle, hip and stepping strategies are examples of postural control strategies in the body. (1) Sensory information is organized and the response created by combining it with environmental conditions and individual factors is updated (Figure 2). (4)

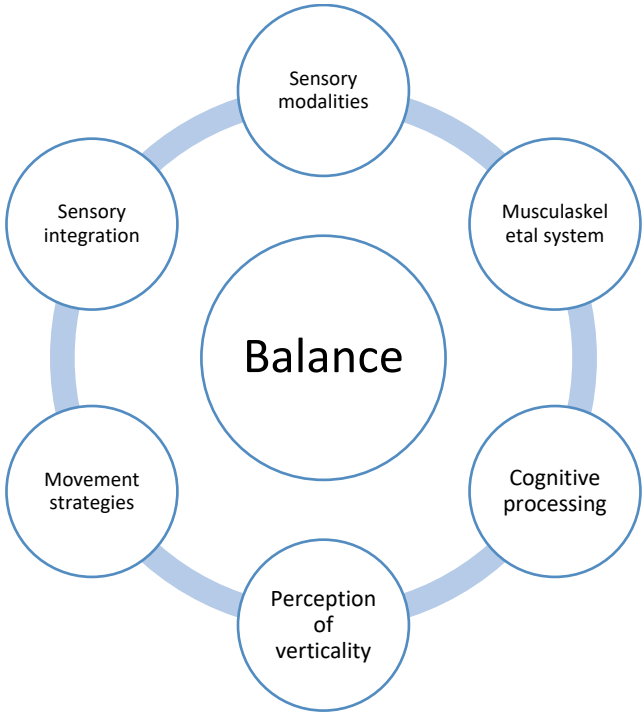

Figure 2: Balance mechanism

2. Postural Control Changes in Vestibular Disorders

The main function of the vestibular system is to detect the position of the head on the body and to maintain balance and postural control along with eye movements. (5) The vestibular system is basically divided into two: peripheral vestibular system and central vestibular system. The peripheral vestibular system consists of otolith organs, semicircular canals and vestibular nerve; The central vestibular system consists of vestibular nuclei and cerebellum, where signals from afferents terminate. Both parts of the vestibular system are involved in maintaining postural control. Vestibular system uses vestibular reflexes to maintain balance and postural control. (6) If one of these structures is damaged, loss of balance and dizziness are among the main symptoms. Vestibular disorders may be involved unilaterally or bilaterally. (7, 8)

Quitschal et al. evaluated the postural control effect in patients with vestibular hypofunction with the interactive posturography system and found that the general stability index and fall index were worse than healthy controls. (9) Apaydın et al. evaluated balance in patients with peripheral vestibular disorders

with the Activity Specific Balance Confidence Scale. Measurements taken at the end of the study found that balance scores were lower than the control group. At the same time, a correlation between balance scores and quality of life has been determined. (10) Many different vestibular exercise programs are applied to improve the symptoms of lost vestibular function in vestibular insufficiency. Meldrum et al. He used classical vestibular rehabilitation and virtual reality applications in patients with unilateral loss. Although the balance improved in both groups in the measurements taken after the 6-week intervention, no significant difference was observed between virtual reality applications and classical vestibular rehabilitation. (11) It has been observed that there are many different methods in vestibular rehabilitation. Such as telerehabilitation exercises, virtual reality exercises, visual stimulus, balance exercises. (12-14) All of these methods have been shown to provide positive contributions to balance, but there is no consensus on their superiority over each other.

3. Postural Control Changes in Cortical Disorders

For balance control, the central nervous system mechanically activates synergistic muscles in the relevant joints to ensure that forces occurring in one joint do not create instability in another part of the body. Many structures are involved in this process, and their main function is to receive and interpret sensory signals coming from the whole body and send commands to the muscles required for stability. Central nervous system structures that play a role in posture control; posterior parietal area, primary and secondary motor cortex, cerebellum, basal ganglia, spinal cord and brainstem. (15) Disorder in any of these structures causes postural control to be affected.

Although the primary injury that occurs in cerebral palsy (CP), where muscle tone, posture disorders and inadequacy in movements are the main problems and is usually accompanied by sensory, cognitive, communication, perception, behavioral disorders and seizures, is not progressive; Functional disabilities and severity of disability are progressive. (16) Children with CP often exhibit poor postural control. (17) A lesion occurs in the central nervous system in a child with CP and prevents the proper functioning of the postural control mechanism. (18) This situation occurs in the child with CP as reciprocal innervation deficiency, tone changes, abnormal coordination patterns and lack of fixation. In order for the child to achieve proper postural control against gravity, muscle tone must increase to the extent of resisting gravity and sufficient muscle strength must be released, so that the desired movements can be made

in a controlled manner. (19) The primary causes of problems in postural control adjustments seen in children with CP are muscle strength deficiency, agonist/antagonist co-activation ratio, incoordination of joint segments, and inadequacy in the firing of motor units responsible for coordinated postural responses. (20) In children with CP, the effects of the corticospinal tract and venteromedial parts disrupt the trunk organization for postural control. Instability in the trunk may cause disruption of body alignment and limitations in postural capacity. (21) In terms of the functional level at which postural control is organized, only the severe forms of children with CP who cannot sit independently cannot exhibit direction-specific postural adjustments. Children with CP at school age and before have permanent dysfunction in postural adjustments at the desired level. The earliest activation in the cranio-caudal direction occurs with the use of neck extensor muscles. This is generally observed in children with mild-to-moderate forms of CP rather than in those with severe forms. It may indicate that the priority of activation in the cranio-caudal direction is the child's strategy to overcome inadequate postural control. Head stabilization in space, as an activation strategy in the cranio-caudal direction, constitutes an important point of postural control. (22) In other words, deficiencies in head and neck control in children with CP cause disruption of the smoothness of the body and head and neck. However, rotational movements that provide smoothness between the body and the head and neck can activate correction reactions and provide some control of movements. (23) It may cause deficiencies in movement and posture control in children with CP, which sometimes persist persistently and sometimes do not appear at the normal time; There are also tonic reflexes such as compound reactions, positive and negative support reflex, tonic labyrinth reflex, tonic neck reflexes. (15)

People who have had a stroke have poor postural control. While sitting, the center of pressure in these individuals shifts more both anteriorly and posteriorly and medially and laterally. (24) Stroke patients have problems in maintaining postural control due to reasons such as posture disorders, muscle strength inequality and inadequate weight transfer. Decreased postural control in stroke patients; It also negatively affects balance, mobilization, activities of daily living and cognitive functions. (25, 26) Among the sensory and motor disorders that develop as a result of stroke, the problem that most affects the independence of patients in their daily lives is inadequate postural control. (27) After stroke, postural control becomes more sensory-oriented rather than anticipatory because the predictive mechanism involves many cerebral structures: cortical

(supplementary motor area and premotor area), subcortical (central gray nuclei and thalamus), and subtentorial (vestibular nuclei and cerebellum). (28) In a study conducted to compare the postural control of healthy elderly individuals and individuals with stroke, displacement of the center of pressure with eyes closed was poor in both groups, but elderly individuals with stroke showed worse results in static and dynamic postural control. (29) In a study conducted to examine the relationship between depression, postural control, pain, the affected side and kinesiophobia in stroke patients, it was observed that as the level of kinesiophobia increased, there was a decrease in postural control. (30) Trunk position sense, an important component of trunk postural control, has been shown to exhibit more trunk repositioning errors in people with post-stroke hemiparesis than age-matched controls. (31) In the study conducted to determine the effect of visual and spatial hemineglect on impaired postural control in the acute phase of stroke, it was shown that hemineglect independently contributed to the deterioration of postural control in the acute phase of stroke. (32) In another study, it was observed that the degree of forward head posture while sitting was directly proportional to sitting postural control and inversely proportional to the degree of kyphosis in sitting after stroke. Additionally, postural control in sitting after stroke has been reported by Brunnstrom to be directly related to the stage of recovery in the affected upper extremity during sitting. (33)

4. Postural Control in Cerebellar Disorders

The cerebellum accounts for 10% of body weight but contains 60-80% of all neurons. (34) The main functions of the cerebellum are muscle tone, motor control of limb movements, walking coordination, motor and nonmotor functions, and oculomotor control related to eye movements. (35, 36) Although the cerebellum has many different functions, it is basically responsible for regulating motor functions. This regulation involves sequential, rhythmic contractions of agonist-antagonist muscles. Main features of cerebellar dysfunctions; tone changes (hypotonia), decreased organization and coordination of skilled movements (dysmetria, tremor, dysdiadochokinesia), speech disorders (dysarthria), gait disorders, eye movement disorders and postural control deficiency. (37)

Postural control consists of the combination of postural orientation and postural stability. It is defined as the ability to control body position in space. Postural orientation is the ability to maintain the connection of body segments with each other and the body with the environment during an action. Postural

orientation occurs through the combination of postural tone and posture. Spatial orientation in postural control; It is based on the interpretation of convergent sensory information received from somatosensory, vestibular and visual systems. (38) Postural stability is known as balance and is defined as the ability to keep the body's center of gravity within the support surface. Postural stability involves the coordination of sensorimotor strategies to stabilize the body's center of gravity during both internal and external perturbation. (38, 39)

Each region of the cerebellum, which is divided into three regions as spinocerebellum, vestibulocerebellum and cerebrocerebellum, contributes to postural control by undertaking different tasks. Although the spinocerebellum consists of the combination of the vermis cerebelli and the intermediate line, this area mostly receives information from the vestibular, pontine and reticular nuclei in the spinal cord and brainstem, and sends projection fibers to the vestibular and reticular nuclei, thalamus, medulla spinalis and cortex. It limits the degree of voluntary movement by stimulating agonist muscles and sending information back to the motor cortex to inhibit antagonist muscles. It helps postural control by providing motor control of trunk and extremity muscles, maintenance of initiated movement and tone regulation (40) In its lesions, a "drunken sailor" gait with a large support. surface, called truncal ataxia, is observed, which is characterized by uncertain start-stop, lateral deviation, unequal steps and gait ataxia. (41) Vestibulocerebellum covers the flocculonodular lobe and is mostly connected to the vestibular nuclei. Information coming from systems related to balance and vision is effective in ensuring and maintaining postural stability and regulating vestibular reflexes through the efferents of the vestibulocerebellum with the vestibular nuclei. Vestibulocerebellum provides control and coordination of head-eye movements. In its lesions, eye movement disorders, nystagmus, vestibulo-ocular reflex dysfunction, posture and gait disorders are observed. The cerebrocerebellum covers the lateral divisions of the cerebellar hemispheres. After the impulses coming to this region from the contralateral cerebral cortex via the pontine nucleus are evaluated, they travel to the thalamus and the premotor and motor areas of the cerebral cortex via the dentate nucleus. Cerebroserebellum; regulates the planning, initiation and timing of movement. (40) In its lesions, impairment occurs in the execution of voluntary and planned movements by the extremities. Disorders such as intention tremor, abnormalities in writing, dysarthria, dysmetria, abnormality in alternative movements, rebound phenomenon and hypotonia are observed. (42, 43) Increased postural sway is typical in cerebellar lesions. Oscillations

vary depending on the location of the lesion. In anterior lobe lesions, postural oscillations of high speed and low amplitude are observed in the antero-posterior direction, while in vestibulocerebellum lesions, postural oscillations of low frequency and high amplitude are observed in all directions. Lateral cerebellar lesions are characterized by minimal postural oscillations that are indistinguishable from healthy individuals. (44)

Bart et al. They evaluated the postural sway of individuals in 11 different tasks for standing and walking. They concluded that the postural oscillations of ataxic individuals were higher and faster than healthy individuals, and that these oscillations were in all directions, not in one direction, especially in patients with lesions in the spinocerebellar region. (45) In a study examining the relationship between trunk position sense and postural control loss in ataxic individuals, it was observed that there was a relationship between trunk position sense and postural control loss. It was concluded that loss of postural control, which is the most important reason for activity and participation limitation in ataxic patients, is affected not only by motor disorders but also by sensory disorders. (46)

Multiple Sclerosis is a chronic demyelinating disease accompanied by motor and cognitive symptoms. When we look at motor symptoms, there may be muscle weakness, coordination disorders and postural effects. (47) In a meta-analysis study evaluating loss of postural control in individuals with Multiple Sclerosis, it was shown that there were significant deficiencies in postural control compared to healthy controls. (48) Cameron et al. They revealed that the stability limits of Multiple Sclerosis patients were inadequate compared to healthy individuals and investigated the cause of falls in Multiple Sclerosis patients. They emphasize that approaches that increase somatosensory input will correct these disorders and reduce patients' risk of falling. (49) In a study examining the relationship between cognitive function and postural control in Multiple Sclerosis patients, it was seen that cognitive function had an effect on postural control. (50) Another study showed a relationship between trunk performance and postural control in Multiple Sclerosis patients. (51)

5. Conclusion

Studies in the literature show that there is a loss of postural control in individuals with different vestibular, cortical and cerebellar involvement. Loss of postural control, which is the determining factor for active participation in daily life activities, is a parameter that should be emphasized during the evaluation and treatment phase.

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CHAPTER XVIII

EFFECT OF EXERCISE ON COGNITIVE FUNCTIONS

Dilan DEMİRTAŞ KARAOBA[1]& Gülfem Ezgi ÖZALTIN[2] & Havva ADLI[3]

[1](PhD), Inonu University, Faculty of Health Sciences, Physical Therapy and Rehabilitation, Malatya, Turkey, E-mail: dilandemirtas92@gmail.com, ORCID: 0000-0002-6754-9335

[2](PhD), Inonu University, Faculty of Health Sciences, Physical Therapy and Rehabilitation, Malatya, Turkey, E-mail: gulfemezgi@gmail.com ORCID: 0000-0003-1591-4844

[3](Lecturer), Inonu University, Vocational School of Health Services, Department of Therapy and Rehabilitation, Malatya, Turkey, E-mail: h.adli@hotmail.com, ORCID: 0000-0002-4802-9131

1. Introduction

Cognitiveness comes from the root knowing; It means 'related to cognition, related to the functioning of intelligence, cognitive'. (1) Cognition is our mind's ability to learn, process and evaluate information. It contains connections related to different cognitive issues such as identifying and solving problems, reasoning, and learning new things. Each of these serves a different function in processing and perceiving information in our minds and are interconnected. (2) Cognitive functions are mental processes that help us perceive events that occur independently of us, choose what is useful to us, store what is necessary, correct it so that it can be used, and develop it. Cognitive disorders are; These can be listed as slowing down in cognitive processing

speed, learning, memory and management difficulties. In addition, losses such as depression, decreased quality of life, and decreased independence in daily living activities are also observed. (2)

Cognitive dysfunction has great clinical significance and has long-term effects on the patient's activities. Pharmacological (antidepressants) and non-pharmacological (exercises, cognitively focused treatments) interventions are being developed that focus predominantly on learning and memory and potentially ameliorate cognitive depression in the brain. (3)

Exercise has many direct and indirect effects on our thinking skills and memory. Regular physical activity has been shown to improve cognitive functions and increase academic success in school-age children and teenagers. (4, 5) In addition, it has been shown in various studies that the rate of loss of cognitive functions can be slowed down with regular physical activity during adulthood and old age. (6, 7) Studies have shown that exercise produces effective results in spatial memory and learning through the hippocampus. The hippocampus has the ability to maintain its plasticity even in adulthood. Therefore, it is possible to stimulate the hippocampus with exercise and lifestyle changes. Many studies have reported that exercise improves cognitive functions in different populations. (8-10) The underlying mechanisms by which exercise improves the structure and functioning of the brain and therefore cognitive functions are; It can be explained as increasing neurotrophin levels, increasing neurogenesis and vascularization, balancing neuroinflammation and ensuring neuronal integrity. (11, 12) High physical fitness achieved through exercise increases brain volume and also improves the functional connections of the nervous system. (12, 13) Exercise also accelerates mental processes in children by stimulating cerebral blood flow and synaptic activities. (14, 15) Therefore, this section aims to briefly summarize the literature on the effects of various exercises on cognitive function.

2. Effect of Aerobic Exercise on Cognitive Function

Aerobic capacity is the ability to deliver oxygen to skeletal muscle through the cardiopulmonary system to provide energy to the relevant muscles during exercise. Aerobic exercise aims to increase the endurance of the cardiovascular system and skeletal muscles by exercising large muscle groups at moderate and high intensity for a long time. (16) It has been proven that aerobic exercise has a positive effect on different systems of body functioning. It has been shown that it regulates blood pressure, endothelial function, inflammation, oxidative stress,

and hormonal responses and has positive effects on cognitive functions. (17, 18) Two structures play a role in the development of cognitive activities with exercise: It increases the growth ability of cells (by enabling them to act like stem cells) and increases the release of a neurotransmitter called BDNF (brain-derived neurotrophic factor). (19) To understand these better, it is necessary to talk about plasticity (neuroplasticity).

Plasticity is the organism's ability to renew itself using existing environmental conditions. Neuroplasticity is defined as the self-renewal of the central nervous system with the change of behavioral, environmental, motor, and sensory factors, as well as thoughts and emotions. (20) Plasticity is based on both structural and functional change. Structural plasticity is referred to as neurogenesis and neural migration. Functional plasticity is the permanent change in learning and memory through the differentiation of synaptic connections. It depends on structural and biochemical changes. (21) Depending on the intensity and duration of the signal arriving at the synapse, the "use it or lose it" principle is used in synapses. Here, synapses that are used more frequently become stronger, synapses that are less used become weaker, and those that are not used disappear. Synaptic connections are made by developing new receptors, or by structural changes in existing receptors and new neurotransmitters. These pathways are sufficient for short-term memory development. (22) Stronger and longer-lasting stimuli are needed for long-term memory development. These are: lengthening of dendrites, increase or decrease in branching in dendrites, formation of new synapses, decrease or increase in existing synapses, pruning of unused dendrites, new neuron formation, neuron death, increase or decrease in brain metabolites, increase in the resistance of neurons to stress, increase or decrease in the post-synaptic structure of neurons. Changes in their activities occur with changes in the levels of neurotrophic factors. (23-25)

Many studies have been conducted showing that neuroprotective activity in the body increases with exercise. Increased neuroprotective activity is also directly linked to cognitive activity. This connection is provided by the hippocampal neurogenesis process. (26) It has been observed that the size of the hippocampus increases with exercise. BDNF, one of the neurotrophic factors, is synthesized during exercise and plays a role in functions such as proliferation, differentiation, maturation, or plasticity in neurogenesis. (19) During aerobic exercise, proteins secreted from large peripheral muscles and metabolic products such as irisin accelerate BDNF expression in the hippocampal region. BDNF crosses the blood-brain barrier and mediates neurogenesis formation and memory recovery together with neuroendocrine factors. (27)

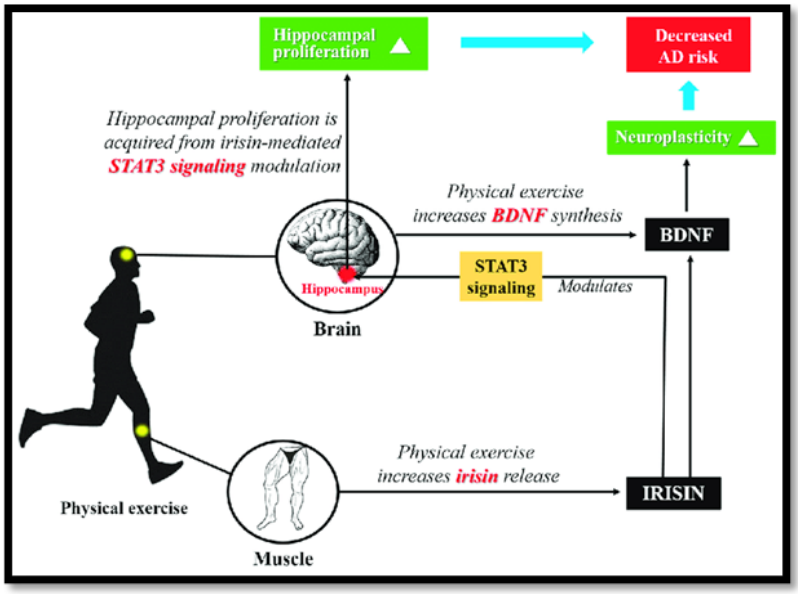

Figure 1. Exercises and brain activity (28)

Studies on the duration and intensity of exercise have shown that although moderate aerobic exercise has short-term positive results, long-term exercises are more effective in hippocampus-dependent learning and the permanence of what is learned. (29) However, it has been concluded that reactive oxygen species (ROS), which are metabolic products during intense exercise, can cause cell damage in both rats and humans. (30, 31) It has been stated that moderately long-term exercises provide more effective results for the effects of aerobic exercise on cognition.

The effects of aerobic exercise have been discussed in many different fields. Zhang et al. examined the effects of aerobic exercise training on cognitive function in patients with depression. He applied for 8-week treatment and was evaluated with neuropsychiatric tests. As a result, there was a significant improvement in many subgroups of neuropsychiatric tests and depression scores in the measurements taken at the 4th and 8th weeks compared to the control group. (32) Evidence-based studies are showing that aerobic exercise improves cognitive function in elderly individuals. The underlying reason for this can be attributed to multiple factors. When the literature was examined, no clear results were recorded. Many variables such as age, hormonal factors, and gender may play a role. (33) Exercise has been shown to have anti-depressant effects and

play a role in combating disease- or age-related mental disorders and atrophy, such as Alzheimer's disease or dementia.

As a result, we can say that moderate-intensity, long-term aerobic exercise positively affects cognitive function by increasing hippocampal activity and is an exercise option that can be used safely in many different diseases, from pediatric groups to elderly groups.

3. Effect of Resistance Exercises on Cognitive Function

A frequently recommended physical intervention strategy to counteract impairment in both physical functioning and cognition is the ongoing and regular practice of resistance exercises or resistance training. (34, 35) However, the neurobiological mechanisms underlying resistance exercise-induced improvements in cognitive functions are not yet fully understood. (36) In the possible mechanism, molecular and cellular changes first occur, which are summarized in the "neurotrophic hypothesis". (37) The "neurotrophic hypothesis" reports that in response to physical exercises (resistance exercises), there is a marked release of different neurochemicals (brain-derived neurotrophic factor [BDNF]). (38, 39) Significant release of specific neurochemicals triggers complex neurobiological processes that lead to functional or structural brain changes that facilitate recovery in cognitive functions. (40, 41)

Numerous biochemical pathways, including as BDNF, fibroblast, vascular endothelial growth factor, and insulin-like growth factor (IGF-I), have been implicated in the relationship between exercise and cognition. (42) However, IGF-1, in particular, is the important factor linking resistance exercise training to cognition. IGF-1 has been demonstrated in studies to enhance synaptic plasticity and neuronal survival, hence preventing the loss of brain tissue and enhancing cognitive function. (43) Furthermore, a number of studies have demonstrated that reduced blood viscosity inhibits the flow of oxygen and nutrients to the central nervous system and has a detrimental effect on cognitive function. Additionally, resistance training has been demonstrated to improve blood flow (44); There have been reports linking this to cognitive function. (45)

Moderate-intensity exercise is known to be the most effective intensity for improving cognitive functions, including memory and learning. Nonetheless, there is disagreement over how high-intensity exercise affects cognitive abilities in comparison to moderate-intensity exercise. High-intensity exercise was shown to have lower oxygenation and inferior cognitive performance when

compared to moderate-intensity exercise and controls in a study that looked into the impact of high-intensity resistance exercise on cognitive processes. (46) Contrary to this study, Cassilhas et al. included 62 elderly individuals in their study to examine the effect of resistance training at two different intensities on cognitive functions in the elderly for 24 weeks. The results of the study revealed that the beneficial effects of medium- and high-intensity resistance exercise training on cognitive functioning were similar. (45)

High-speed resistance exercise, balance exercises, and band stretching exercises were used in the study investigating the effects of resistance exercise training on cognitive function and physical performance in older persons with cognitive weakness. The findings demonstrated that in older persons with cognitive impairment, high-speed resistance training was beneficial in enhancing both physical and cognitive function. (47)

In a study examining the association between strength exercise intensity and cognitive function, 68 participants were divided into control and 40%, 70%, or 100% 10-repetition maximal resistance training groups. The findings indicate that resistance exercise intensity and cognitive function have a dose-response connection. High-intensity exercise has an impact on processing speed, whereas moderate-intensity exercise has the most positive effects on executive function. (48)

Resistance training was discovered to be an effective way to boost cognitive function in healthy individuals right away in a study examining the impact of a single resistance exercise session on cognitive performance in those adults. (49)

A comprehensive evaluation was conducted to assess the impact of resistance training on cognition in older adults with and without moderate cognitive impairment. The study's findings demonstrated that resistance training improved the executive function and overall cognitive function of the elderly while having minimally beneficial effects on memory and attention in short-term interventions. It was discovered that the level of attention had not much improved. Furthermore, it was discovered that resistance training conducted every three weeks outperformed training conducted every two weeks in terms of overall cognitive performance. (50)

A meta-analysis looked at how resistance training affected cognitive function. The findings indicated that resistance training improved executive functions, composite cognitive scores, and screening tests for cognitive impairment, but had no appreciable impact on working memory. (51)

4. High-Intensity Interval Training and Cognitive Function

The stimuli that the individual receives from his environment are received by the sensory organs and perceived in the brain. After these stimuli are perceived, the process of understanding and interpretation begins and this process takes place in the brain. After the data is interpreted and given meaning, it is stored in the brain as experience. In later processes, this data is used for the reactions we will give at the appropriate time. Cognitive state is defined as a reaction process in which the stimuli we receive are transmitted to the cortex and affect our behavior and attitudes. Each area of the brain has its own functions. However, no region works independently of the other region, they perform their functions in harmony with each other. Maintenance of cognitive functions also occurs as a result of this adaptation. Memory, perception, judgment, foresight, awareness and executive functions are examined within cognitive functions. (52)

Exercise has long been associated with cognitive performance, and many studies find that healthier people perform better at cognitive tasks. This highlights the relationship between exercise and long-term cognitive impact. (53) Moderate-intensity sustained aerobic exercise also provides better developed instantaneous speed processing, selective attention, aspects of inhibitory control, short-term memory, and selective attention. (54, 55) Despite the positive effects of exercise, the biggest obstacle to regular exercise is thought to be a waste of time. (56) In recent years, high-intensity interval training (HIIT), characterized by repeated sessions of high-intensity exercise combined with recovery and low-intensity exercise, has attracted increasing attention as a time-saving method. (57) High-intensity interval training programs are known to have positive effects on health and performance by increasing aerobic and anaerobic capacity with high time efficiency. (58, 59) In addition, recently there have been increasing studies showing that HIIT has a positive effect on cognitive functions by positively affecting neuroplasticity. (60, 61)

HIIT positively affects cognitive function by affecting neuroplasticity markers in the cortex and hippocampus. (62, 63) Winter et al. In their study, they found that a single HIIT session accelerated word learning in athletes by 20%, as opposed to moderate exercise. In the study, they stated that the positive change in BDNF, dopamine and epinephrine levels were important mediators through which the retention of new vocabulary could be improved. (64) There are also studies in the literature that do not associate positive developments in cognitive function as an acute effect of HIIT with BDNF level. (65, 66) The acute

phase of HIIT can regulate complex motor movement by improving motor skill acquisition and memorization in parallel with the increase in some biomarker concentrations (IGF-1, VEGF, BDNF). (67) Additionally, a higher-intensity exercise session performed immediately before or after the execution of the motor task is more effective than a single moderate-intensity exercise session for increasing long-term retention of the motor skill on both days 1 and 7 following learning. (68) According to a meta-analysis study examining the effect of HIIT on cognitive function and mental health in healthy children and adolescents, there is evidence suggesting that HIIT can improve cognitive function and mental health, but due to the insufficient number of studies and heterogeneity in the methodology part of the studies, higher studies are needed to confirm these findings. It has been stated that there is a need for quality research. (69) The study examining the effects of different volume HIIT protocols on cognitive performance in healthy individuals shows that low and medium volume HIIT have similar effects on post-exercise executive function measurements. As a suggestion, the authors concluded that the HIIT volume required to reveal executive function performance gains may be lower than suggested by previous research. (70)

Although there were improvements in cognitive function after 8 weeks of HIIT training in the geriatric population, this was not associated with hippocampal area volume. (71) In another study conducted in the geriatric population, HIIT, aerobic exercise and resistance exercise were given to different groups and their effects on physical and cognitive functions were investigated. Physical function was evaluated with the time up go test and submaximal Bruce treadmill protocol, and cognitive function was appraised with the Stroop Test. As a result of the study, aerobic exercise and resistance exercise were superior to HIIT in improving the executive cognitive function of elderly individuals; HIIT, on the other hand, has been shown to be most beneficial in improving information processing speed and also provides the greatest gains in physical function. (72) Studies have shown that lactate is secreted by active muscles during a HIIT session applied to healthy individuals and individuals with stroke. (73, 74) In healthy individuals, increases in blood lactate concentrations often lead to increases in serum BDNF levels. This situation is also associated with motor cortex excitability and motor learning. (75) In a study examining the effect of HIIT on cognitive functions after stroke, it was observed that HIIT training added to conventional treatment had a positive effect on cognitive functions evaluated with the trail making test. (76) Recent studies have reported

promising effects of HIIT on cognitive functions in neurodegenerative diseases. In patients with moderate cognitive impairment, HIIT combined with ketogenic diet and memory training may reverse early-stage memory loss. (77) HIIT reduces depression in people with serious mental illness. (78)

When the studies are examined, it is seen that HIIT provides positive improvements in cognitive function through different mechanisms, however, the studies in the literature are methodologically heterogeneous. It is thought that more comprehensive and long-term studies on the subject are needed.

5. Dual Task Exercises and Cognitive Function

Dual task methodology is based on performing cognitive or motor tasks simultaneously. This approach includes the ability to perform motor and cognitive tasks in daily life, primarily while walking or maintaining postural balance. (79) To achieve DT (dual task) performance, activation of multiple cortical areas is needed. It is thought that cortical-neural degeneration occurring in neurological diseases causes impairment in demanding tasks. In functional MRI (fMRI) imaging, it was observed that there was more activation in the supplementary motor area and prefrontal area in dual task walking compared to single task. (80, 81) Another imaging study investigated neural connections during walking, talking, and both. Depending on the degree of difficulty, activation in motor areas was recorded to be higher during speech while walking and lower only during walking. This activation was seen in the cerebellum, supplementary motor area, prefrontal area and parietal area. (82) Executive control networks responsible for paying attention to task demands; It has been associated with the anterior cingulate, prefrontal cortex, parietal cortex and other frontal brain regions. In neurodegenerative diseases, there is a loss of neurons in the aforementioned attention and executive function networks. Executive functions are responsible for the integration of sensory information and motor planning required to maintain balance in dynamic activities such as walking and posture (81, 83) Impairment in DT performance due to adaptation to challenging tasks in neurodegenerative diseases is due to loss of executive functions. (81) Due to deterioration in dual task performance, there is an increase in the risk of falling, deterioration in quality of life and decrease in functional abilities. (84) Many activities of daily life involve performing several tasks simultaneously and require attentional capacity to maintain both motor and cognitive functions. Given that attentional capacity is limited, demands

exceed capacity and the same tasks affect dual-task performance. It is said that if attention capacity is exceeded during multitasking, one or both of the tasks will be impaired. (85) One of the most important reasons for this is cognitive dysfunction. Impairment in executive functions and attention deficits negatively affect dual task performance in patients. (86) The tasks given in dual task studies are divided into two: motor and cognitive. As an additional motor task, tasks such as catching a ball while walking, carrying a tray, carrying a glass full of water without spilling it, and fastening a button were given. Cognitive tasks are reaction time, decision making and discrimination task, mental monitoring task, working memory task and verbal fluency task. (87) The primary aim of dual task approaches is to improve daily living activities by using the interaction of cognitive function and motor performance. (88) Dual task training aims to improve functional performance by using the interaction of motor and cognitive tasks. The effectiveness of dual task use on cognitive functions such as walking parameters, walking speed, balance, cognitive flexibility and processing speed is being investigated. (89, 90) It is thought that this application can improve cognitive function, especially executive functions. (91)

In a study conducted with Parkinson's patients, the effect of virtual reality training including motor-cognitive tasks on DT performance was investigated. Participants went through a virtual reality maze while performing a cognitive task, and at the end of the study, it was found to be effective on both motor and cognitive functions in patients with gait freezing. (92) In the literature, there are studies in which the difficulty level of the tasks is increased and the obstacles are changed in each session by applying virtual reality training on a treadmill; there are studies showing improvement in dual task performance, a decrease in the number of errors in the verbal fluency test, and an increase in walking speed and step length. (93, 94) In a randomized controlled study comparing dual-task exercises with a traditional exercise group in elderly individuals, it was observed that dual-task exercises affected executive function, gait. (95) 8-week dual-task exercises in elderly with mild cognitive impairment; found it to be effective in improving cognitive and executive functions, attention/working memory, and reducing depression (96) In a study evaluating the effects of dual-task exercises on physical and cognitive function in individuals with neurological diseases, it was found that the exercises were moderately effective on gait, balance and cognitive function. (90) In another study, walking and dual task-based exercises were given to a group for 12 weeks, and no intervention was given to the control group. At the end of the study, it was observed that there was an improvement in memory and executive functions in favor of the exercise group. (97)

Studies in the literature show that motor and cognitive tasks added to activities positively affect cognitive function. Follow-up studies are needed to determine the long-term effect.

6. Conclusion

As a result, it has been observed that exercise programs applied to individuals from various populations produce effective results on cognitive functions. In the literature, more research is needed on different types and different populations regarding the effectiveness of exercise on cognitive functions.

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CHAPTER XIX

BALANCE IN INDIVIDUALS WITH VISUAL IMPAIRMENT

Tuba MADEN[1] & Sedat YİĞİT[2]

[1](Asst. Prof. Dr.), Gaziantep University,
Department of Physiotherapy and Rehabilitation,
E-mail:tuba.kmaden@gmail.com
ORCID: 0000-0001-8713-0825

[2](Asst. Prof. Dr.), Gaziantep University,
Department of Physiotherapy and Rehabilitation,
E-mail:sedat.ygtt@gmail.com
ORCID: 0000-0001-7134-8379

1. Introduction

It is known that there are approximately 405.1 million visually impaired individuals today (1). Vision is one of the basic sensory organs in performing most life activities independently. The visual system is an important source of information in maintaining balance and is the first system that plans our movements and provides information about the external environment (2). During activities, 80-90% of the information is obtained through visual perception, visual perception, and body orientation (3). The vision, proprioception and balance systems are integrated by cortex and a motor response is created during postural control (4). Thanks to the vision, individuals can plan and coordinate movement (5, 6).

There is a relationship between visual impairment and poor balance and quality of life (7, 8). The physical capacities of individuals with visual impairment decrease, and their balance and orientation abilities decrease (9). Individuals without visual impairment can obtain visual information from the environment and make necessary body adjustments according to the information. Visually impaired individuals may experience disruptions in the orientation process due

to lack or lack of visual input. Individuals with visual impairments cannot make the necessary body arrangements due to the lack of visual information during activities such as changing places, public transportation, going up and down stairs. For this reason, visually impaired individuals experience limitations in their mobility and participation in daily life activities is affected (10).

2. The Role of Visual Inputs in Balance

Balance is defined as the ability to maintain the body's center of gravity within the support surface and maintain postural stability and orientation during movement or stance. The postural control system has two main functions: postural stability and postural orientation. Postural stability describes the ability to control the body's center of mass within the support surface; The alignment of the segments with the stimuli from the environment, the adjustment of the alignment, and the stabilization of the necessary segments explain the postural orientation. Postural control is the control of the body's position in space for the purpose of stability and orientation. Every task in our daily life actually requires postural control because it requires stability and orientation. The postural control system occurs through the interaction of the musculoskeletal system and nervous system. Neural components are essential for postural control. These;

a. Motor processes that regulate muscles and muscle synergies in the body,

b. Specialized sensory systems (visual, vestibular, somatosensory) and sensory integration,

c. Mapping from sensation to movement involves the prospective cognitive source of control and higher-level cognitive processes (preparatory and adaptive postural control).

It emerges through individual-environment-task interaction involving postural control systems (11). Information from the visual, somatosensory and vestibular systems provides information about the body's position in space (Figure 1). When the direction of movement changes suddenly, warnings that help the head adapt to different directions are received by the visual system. Thus, by ensuring that the gaze is kept constant by the whole of the visual systems, the sense of position of the body in space, that is, balance, is provided. The visual system provides a significant part of the sensory support of the vestibular system. The visual system continuously receives efferent information from the vestibular system and continuously adjusts eye movements according to head and body position (12). The signals that occur with every sudden turning movement of the head come to the eyes from the semicircular canals, so the eyes move in the opposite direction of the head rotation and at the same rate (13). These inputs

are processed and integrated with the most reliable sensory strategies for a given task and environmental condition. Centrally integrated information must elicit sufficient motor responses to maintain balance. These answers are organized as motor strategy. Five basic parameters have been defined that play an important role in maintaining balance (Figure 2) (14). In order to ensure the continuity of information in individuals with visual impairment, the development of the somatosensory system and vestibular system is necessary. Accordingly, the importance of somatosensory and vestibular sensory inputs increases in maintaining stability and orientation in visually impaired individuals (15, 16).

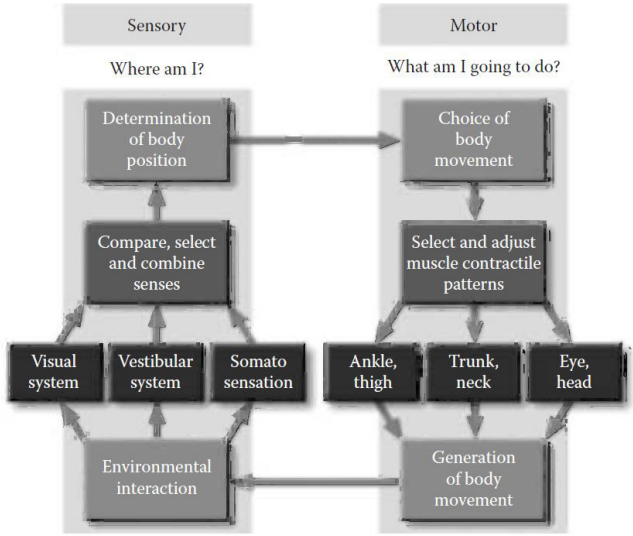

Figure 1. Balance's sensory-motor control (14).

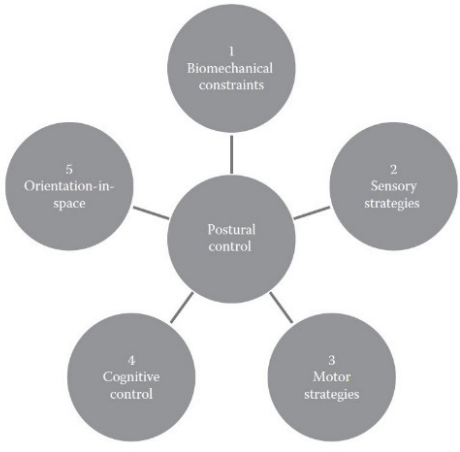

Figure 2. Basic parameters in postural control (14).

Proprioceptive inputs obtained from the somatosensory system are more prominent than other sensory systems in maintaining balance in visual impaired individuals. Moreover, visual impaired individuals are thought to develop higher abilities to use their other senses compared to healthy individuals. It has been shown that in visual impaired individuals, other capacities develop in the regions belonging to the visual areas due to cerebral plasticity. The development of the visual cortex with different senses to compensate for sensory information is called Cross-Modal Plasticity (17).

3. Kinesthetic Perception in Individuals with Visual Impairment

People who are blind rely on their senses of smell, touch, and hearing to do daily tasks. High kinesthetic awareness is therefore necessary for the vision impairment. Kinesthetic perception serves as a vital source of input for blind individuals on movement features, including direction and position in space (18). Through stages of practice that continuously develop sense, kinesthetic awareness of abilities will enhance, refine, and include tool-based work motions. These stages also form levels of vision and postural stability, which are developed as a result of kinetic sensory perception and muscular ability (18). Kinesthetic sense is not well developed, and it can be challenging to maintain control over one's posture and movement. However, if the motion is accurate and on aim, there is a propensity to carefully manage your movements while maintaining the same stance or action. This is because a person with high kinesthetic awareness will undoubtedly be able to control the movement and position that have been performed. One of the main advocates of efficient movement is carefully regulated movement (18). The cycle of evaluating afferent signals in the reference system supplied by efferent processes can be understood as kinesthetic perception (19). The perceptual process leads to perception. Three different types of functions are involved in the perceptual process when processing a stimulus: 1) detection, 2) comparison, and 3) recognition. The term "kinesthetic perception" describes the receptors found in tendons and muscles that enable us to perceive our bodies' positions (20). Kinesthetic learning refers to the variation in body component position and motion based on visual, auditory, and linguistic cues. The ability of the human body's organs to discriminate between he way the limbs and body are positioned and moved, both actively and passively, is known as kinesthetic perception or kinesthetic sense. The process of detection involves trying to determine if any

stimuli are entering the body through the senses. The goal of comparison is to determine the degree to which freshly input stimuli match stimuli that were previously received. Pattern orientation and the type of incoming stimuli are related to recognition. The degree of sharpness with which the body's location and movement are felt through the senses is reflected in the perceptual process's sharpness. Kinesthetic, or proprioceptive, awareness of the body in space and its connection to its components is demonstrated by the feeling of motion (18). Kinesthetic perception is necessary for blind persons to get input about the properties of their movements.

4. Balance in Individuals with Visual Impairment

It has been suggested that visual impaired individuals rely more on proprioceptors in balance control, while healthy individuals rely more on visual stimuli (21). In a study comparing visually impaired individuals and blindfolded healthy adults, it was shown that visual impaired individuals have a better ankle joint position sense (22, 23). Another study found that visual impaired athletes have better knee proprioception than healthy athletes can be considered as evidence that visual impaired individuals use the somatosensory system more actively (4). However, visual impaired individuals have better proprioception does not mean that their balance is better (22). In the literature, there are studies proving the balance problems and the increased risk of falling for visually impaired people (24-27). The fact that the main sensory system used to maintain standing balance is the visual system may explain these problems (24). It is observed that visually impaired individuals have problems in maintaining balance due to the insufficiency of the stimuli received from the visual system (25-27). Since the visual system provides the opportunity to notice and take precautions in advance about environmental changes that may occur in the support base, visual impairment may reduce the ability to maintain balance and cause falls. Some studies have shown that the risk of fall-related injuries is higher in visually impaired individuals than in healthy individuals (6, 28). Besides, impairments to vision cause people to concentrate more intently on their tasks, which improves postural stability and maintaining accuracy (29). Some views argue that balance can be maintained in a certain environment even when information is not provided from any system, due to the provision of information from more than one afferent signal source (16, 30).

5. Conclusion

Postural stability and postural orientation of individuals with visual impairment are affected separately. Postural control, that is, balance ability, formed by the integration of these systems, was negatively affected compared to healthy controls. Visual deficits, which are one of the basic sensory inputs in establishing balance, cause increased use of somotasensory senses and proproception. Thus, the kinesthetic perception and body awareness of visually impaired individuals change.

Considering all these, it should not be forgotten that the balance of visually impaired individuals is affected and the kinesthetic perception, proprioception and body awareness are also affected due to this influence.

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