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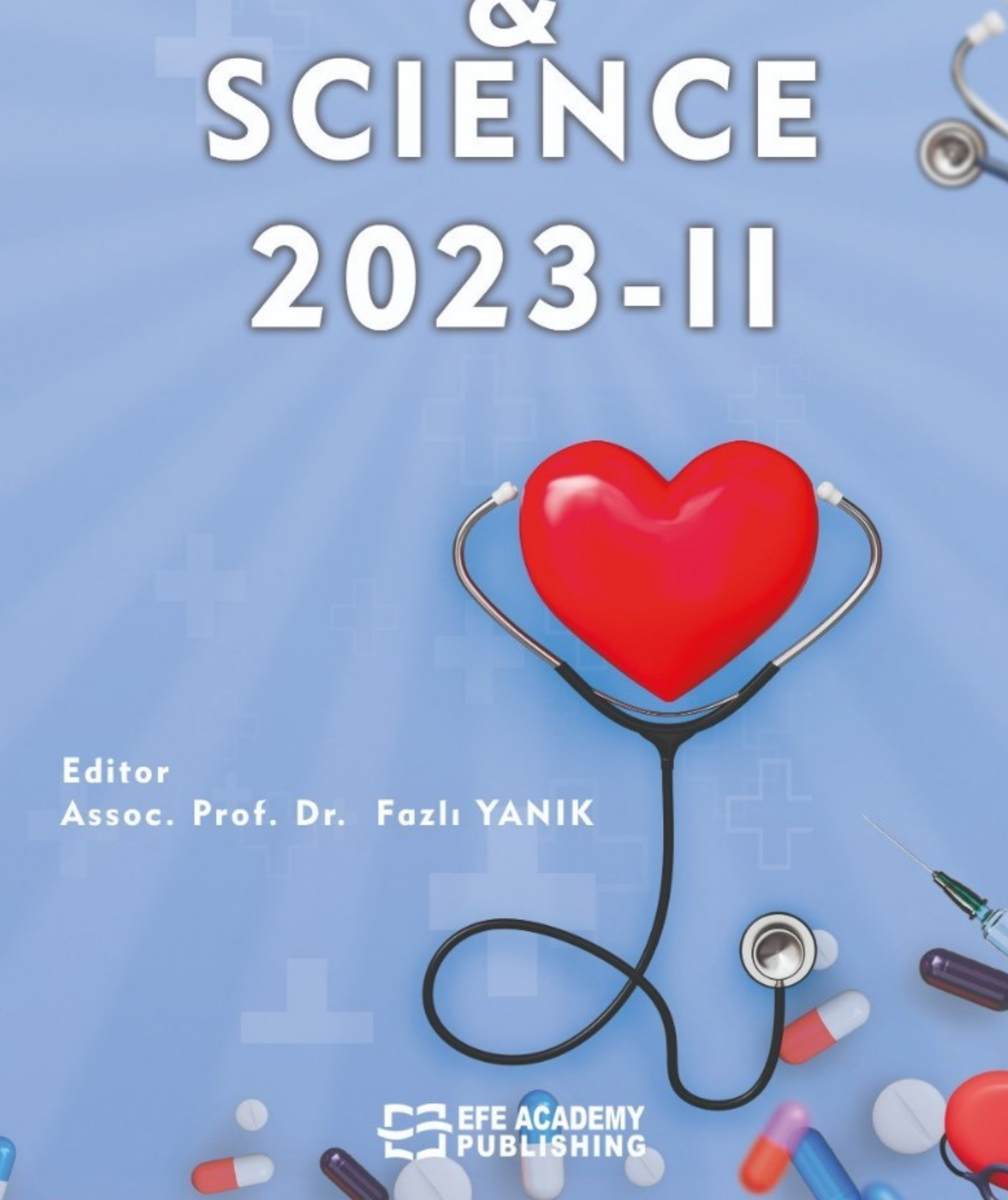

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Assoc. Prof. Dr. Fazlı YANIK
ORCID (0000-0002-8931-5329)

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PREFACE

Health is one of the important issues that people are looking for the most since the day humanity existed. Throughout the human history, health has always been at the center of science and technology, and has also guided science and technology. In this respect, health has been the field of science that scientists have studied the most from past to present.

Specialization has an important place in the development of science. Today, there are many different fields of science under the umbrella of Science and Social sciences, which are basic sciences. Health is the science that interacts most with the sciences in these basic fields. For this reason, health sciences is a multidisciplinary science that is highly related to other sciences.

Health sciences have a wide range of subjects both because of their many sub-disciplines and because they are related to other sciences. However, it is very important to have basic and up-to-date knowledge with a multidisciplinary approach in this broad scope in the development of scientists and employees in the field of health. For this purpose, with the book series of Health & Science, we aimed to compile scientific studies from different disciplines of health sciences in our country and to convey basic and current information to our valuable readers.

We sincerely thank all chapter authors for their contributions to the Health & Science-2023-II book.

Editor
Assoc. Prof. Dr. Fazlı YANIK

CONTENTS

CLINICAL VARIANT INTERPRETATION IN GENETICS

Mustafa Tarık ALAY

- Affiliation: Etlik City Hospital, Ankara/TURKIYE
- ORCID: 0000-0002-1563-2292
- Mail: mtarikalay@gmail.com

1. CLINICAL VARIANT INTERPRETATION IN GENETIC

Human genetics is a fundamental science that primarily focuses on three issues: cytogenetics, molecular genetics, and clinical genetics. With technological advancements, novel molecular genetic techniques are much more adapted in current life. Many time and money-consuming technologies are now replaced with novel techniques. However, nowadays, we are facing a unique problem: The actual management of Big Data. The clinical next-generation sequencing (NGS) industry has experienced significant expansion, with the worldwide clinical NGS services market valued at $2.2 billion in 2015 and projected to increase to $7.7 billion by 2020 (Phillips & Douglas, 2018). Many steps of next-generation sequencing techniques are automatized. However, the clinical DNA variant interpretation is the last step of NGS data analysis, and it obligated experienced and skillful interpretation teams. Because clinical variant interpretation steps are necessary for good collaboration with clinical geneticists, molecular geneticists, biologists, bioinformaticians, techniques, and consultant doctors(Barwell et al., 2019; Berwouts et al., 2010), it is essential to understand clinical variant interpretation to make an accurate decision on the patient. However, variant interpretation is a detailed process. In this chapter, we only focus on DNA variant interpretation. While discussing issues of DNA Variant interpretation, we focus on the points we face with routine clinical applications.

2. SEQUENCING TECHNIQUES

Understanding the clinical variant interpretation is only possible by understanding the keynotes on sequencing technologies. The Sanger sequencing technique, introduced in 1977, has been widely regarded as the preeminent sequencing method in clinical laboratory settings. However, the Sanger sequencing technique needs to be improved due to its low throughput and high cost. The term "Next-generation sequencing (NGS)" is commonly referred to as "massively parallel sequencing" in academic literature. The term pertains to high-throughput sequencing technology, which facilitates the sequencing of a vast quantity of DNA templates in parallel, ranging from millions to billions. This process generates unprecedented genetic data in a single run, as cited in the reference. NGS offers several advantages, such as increased sequencing capacity, the capability to multiplex samples, and reduced sequencing expenses when performed in batches (Yin et al., 2021).

The second-generation methodologies, exemplified by the Illumina or Ion Torrent platforms, typically involve DNA fragmentation, DNA end-repair, adapter ligation, surface attachment, and in-situ amplification. Utilizing "short-read" sequencing technologies entails the highly parallel sequencing of brief reads, wherein numerous sequencing reactions are executed concurrently, numbering in the millions. Due to the short length of short-read technologies, sequencing data must be reassembled over long segments of DNA. This is hard to do when there are structural changes or areas with low complexity (Hu et al., 2021).

Third-generation sequencing techniques are widely implemented in nowadays technologies. Two novel sequencing platforms, third-generation sequencers, can generate extended sequencing reads of a solitary molecule. The Pacific Biosciences (PacBio), SMRT (single molecule real-time), and the Oxford Nanopore are these platforms. Both platforms can conduct long reads, with the PacBio averaging 14-40 Kbp and the Nanopore ranging from 8-100 Kbp, with the current Nanopore sequencing record at approximately 2.3 Mb. According to sources, the PacBio technology has reduced the error rate to less than 1%, while the Nanopore technology has reduced it to less than 5%. However, the adoption of these sequencers in clinical laboratories is limited due to their higher cost, lower capacity, and potential difficulties (Yin et al., 2021).

3. GENOMIC MEDICINE AND VARIANT INTERPRETATION

3.1. Genomic Medicine and Variant Interpretation

Advances in genomic technologies have revolutionized the field of medicine, providing unprecedented opportunities to understand the genetic underpinnings of human health and disease. The field of genomic medicine pertains regarding the utilization of genomic data to facilitate patient care, facilitate individualized medical interventions, and enhance health results. The precise interpretation of DNA variants, which serve as the fundamental determinants of genetic variation among individuals, is a crucial factor in the effectiveness of genomic medicine and practical medical applications. The process entails the recognition, categorization, and evaluation of the pathogenicity or importance of DNA variations detected in the genome of an individual. The primary objective of variant interpretation is to furnish clinically significant data that directs patient management determinations,

encompassing diagnosis, prognosis, treatment choice, and genetic consultation(Manolio et al., 2013).

3.2. The Significance of Precise Interpretation of Variants

The precise interpretation of variants holds significant importance for various reasons. Primarily, it facilitates the identification of genetic variants that cause or contribute to monogenic diseases, which are predominantly caused by single DNA variants with substantial effects. Through identification of the precise genetic variation accountable for a patient's ailment, medical practitioners can establish a precise diagnosis and execute suitable approaches for disease management(Alay et al., 2023). Secondly, variant interpretation plays a crucial role in comprehending the genetic risk factors associated with complex diseases like cardiovascular diseases, diabetes, and cancer. Frequently, these circumstances entail the interaction of numerous genetic variations, with each one exerting a minor impact. Through the examination and elucidation of the cumulative influence of these genetic variations, scholars and medical practitioners can discern persons with heightened susceptibility and execute preemptive measures or focused interventions(Manolio et al., 2013). The another significance of variant interpretation is paramount in the field of pharmacogenomics, which endeavors to enhance drug selection and dosage by leveraging an individual's genetic makeup. Genetic variations can impact drug metabolism and response, resulting in variations in both therapeutic outcomes and adverse effects. Through the consideration of genetic variants that are pertinent to drug metabolism and response, healthcare professionals can individualize treatment protocols, reduce unfavorable events, and enhance therapeutic results(Luvsantseren et al., 2020; Russell & Schwarz, 2020). Finally, the importance of variant interpretation lies in its ability to identify and characterize genetic variants that are linked to susceptibility to multifactorial diseases. These diseases arise from a complex interplay of genetic and environmental factors. Through the elucidation of the impact of these variants, researchers can uncover the fundamental mechanisms of disease development and potentially create innovative preventive or therapeutic interventions(Federici & Soddu, 2020).

It is noteworthy that the interpretation of DNA variants in clinical settings encompasses a broader scope than just rare diseases and personalized healthcare. Population-level genomic studies rely heavily on its

crucial role in identifying and interpreting DNA variants, thereby enhancing our comprehension of population genetics, evolutionary biology, and the genetic underpinnings of traits and diseases across a wide range of populations.

3.3. The American College of Medical Genetics and Genomics (ACMG) guidelines

The American College of Medical Genetics and Genomics (ACMG) guidelines are widely recognized and utilized in the field of clinical genetics for the interpretation of genetic variants. These guidelines provide a systematic framework for evaluating the pathogenicity and clinical significance of genetic variants, aiding in accurate diagnosis, prognosis, and treatment decisions. The ACMG guidelines outline various types of evidence that should be considered in variant interpretation, including population data, computational predictions, functional assays, familial segregation data, de novo data, and phenotypic findings(Mighton & Lerner-Ellis, 2022). These guidelines emphasize the importance of combining multiple lines of evidence to assign a classification to a variant, such as pathogenic, likely pathogenic, uncertain significance, likely benign, or benign(Mighton & Lerner-Ellis, 2022).

The application of the ACMG guidelines has been demonstrated in various genetic conditions. For example, in the context of familial hypercholesterolemia (FH), the guidelines were used to classify variants associated with the disease and determine their pathogenicity(Chora et al., 2018) . Similarly, in the field of prenatal screening, the ACMG guidelines have been utilized to guide the use of noninvasive prenatal screening using cell-free DNA (NIPS) (Gregg et al., 2016).To ensure accurate variant interpretation, the ACMG guidelines have been supplemented with disease-specific specifications. These specifications provide additional guidance and evidence criteria tailored to specific genes or diseases of interest(Harrison et al., 2019). This approach allows for a more precise and context-specific interpretation of genetic variants. The ACMG guidelines have also been instrumental in addressing challenges related to the interpretation of multiple pathogenic variants in a single patient. With the advent of multi-gene panels for cancer risk assessment, the guidelines have helped clinicians navigate the complexity of interpreting multiple pathogenic variants and determining their clinical significance(Slaught et al., 2021). Over the years, the ACMG guidelines have evolved to incorporate new evidence and address emerging

issues. For example, the guidelines have been updated to include recommendations for reporting secondary findings in clinical exome and genome sequencing(Ormond et al., 2019). This reflects the dynamic nature of genetic research and the need to adapt guidelines to keep pace with advancements in the field.

In summary, the ACMG guidelines provide a standardized and evidence-based approach to the interpretation of genetic variants. They play a crucial role in clinical genetics by guiding clinicians, researchers, and laboratory diagnosticians in accurately assessing the clinical significance of genetic variants and making informed decisions regarding patient care.

3.1.1. ACMG Criterias

While the American College of Medical Genetics (ACMG) criteria are widely used for the classification of hereditary variants, there are also other criteria used for the classification of somatic, pharmacogenetic, and multilocus hereditary diseases. In this section we only focus on ACMG criterias. The ACMG criteria consist of a total of 28 criteria, with 16 classified as pathogenic and 12 as benign. Pathogenic variants are classified into four categories: strong (PVS1), moderate (PS1-4), supporting (PM1-PM6), and benign variants are classified into three categories: stand-alone (BA1), strong (BS1-4), and supporting (BP1-6)(Richards et al., 2015). The classification of variants based on ACMG criterias were shown in Table 1.

Table 1. ACMG Variant Classification

Variant type	Benign		Pathogenic			
Degree	S (-18.7)	P (-2.08)	P (2.08)	M (4.33)	S (18.7)	VS (350.0)
Population frequency	BA1, BS1, BS2			PM2	PS4	
Computational and Predictive		BP1, P3, BP4, BP7	PP3	PM4 PM5	PS1	PVS1
Functional	BS3		PP2	PM1	PS3	
Segregation	BS4		PP1			
De novo				PM6	PS2	
Allelic		BP2		PM3	PS4	
Others		BP5, BP6	PP4, PP5		PS3	

Note: The classification in Table 1 represents the variant types and their corresponding classification based on data type and strength. The abbreviations used in the table are as follows:S: Strong, P: Pathogenic, M: Moderate, VS: Very Strong, BA1: Stand-alone benign, BS1-4: Strong benign, BP1-6: Supporting benign, PS1-4: Strong pathogenic, PM1-PM6: Supporting pathogenic, PP1-5: Supporting pathogenic

3.1.2. Limitations of ACMG criterias

In fact, the origin of a particular disorder may vary in its manifestation, ranging from a single gene defect with high penetrance to a multifactorial disease. Additionally, the disorder may involve several gene loci that do not have equivalent pathological implications for the disease under consideration. Furthermore, it is important to note that even in genes that are responsible for Mendelian disorders, variants that are clinically significant cannot be easily categorized into a binary system of either being causative or benign(Burdon et al., 2022; Nykamp et al., 2017; Richards et al., 2015). One of the challenges in clinical DNA variant interpretation is the lack of standardized criteria for assessing certain types of variants. For example, mitochondrial DNA (mtDNA) variants have unique features, such as maternal inheritance, variant heteroplasmy, and the absence of splicing, which require specific considerations in their interpretation (McCormick et al., 2020) Similarly, regulatory variants, which can deregulate transcription factor genes and contribute to disease, are underrepresented in current variant classification guidelines(Lee et al., 2020). Efforts are being made to develop specific criteria and frameworks for the interpretation of these types of variants to improve accuracy and consistency in clinical practice. Clingen registry dedicated to solve limitations of ACMG criterias.

THE CHALLENGES IN INTERPRETATING VOUS VARIANTS

Interpreting variants of unknown significance (VOUS) poses several challenges in clinical practice and genetic research. One of the main challenges is the classification of these variants as pathogenic, benign, or VOUS. Different pathogenicity prediction algorithms may provide incongruent results, further complicating the interpretation of non-synonymous variants(Choufani et al., 2015) The lack of available supporting literature or functional analysis for novel missense variants can also contribute to the classification of variants as VOUS(Tanudisastro et al., 2021). This challenge is amplified in ethnically diverse populations, where the interpretation of novel missense variants in individuals with underrepresented ethnic backgrounds remains a challenge(Tanudisastro et al., 2021). Furthermore, the interpretation of VOUS can be particularly challenging when parental samples are not available, as the presence of de novo events can provide valuable information (Armour et al., 2018). The interpretation of VOUS becomes even more challenging when the phenotype

is non-specific or when the clinical significance of the variant is uncertain(Pauta et al., 2022) . In cases where missense variants result in amino acid substitution, classification as VOUS is common due to the challenges in determining their pathogenicity (Kropski et al., 2017) The counseling and management of patients and families with VOUS can be complex and uncertain. The difficulty in interpreting and counseling in cases of VOUS has led to debates about not reporting these variants in certain contexts (Ghi et al., 2016). The interpretation and clinical management of VOUS can also be challenging in prenatal diagnosis, where the identification of novel variants and the determination of their clinical significance can impact decision-making during pregnancy(Pauta et al., 2022).

NOVEL METHODS

Physicians and patients face difficulties in comprehending and interpreting the clinical implications of variants of uncertain significance (VOUS). Functional studies that are well-designed have the potential to assess the clinical implications of the VOUS variant. However, these studies can be resource-intensive in terms of both time and cost. Therefore, there is a need for novel methods that are rapid, cost-effective, and low-risk to predict the effects of variants. Divergent viewpoints are present regarding the selection and quantity of protein prediction techniques and meta-predictors utilized in the assessment of clinical variants. The American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) have suggested examining a limited number of genes or illnesses. However, this approach falls short of accurately forecasting the clinical implications of the vast majority of genes. In order to minimize the uncertainties associated with clinical evaluation, it is imperative to implement innovative techniques. Alay et al. devised a novel technique that was applied to MEFV gene mutations for this objective. The efficacy of this approach surpasses that of all extant ensemble methods. While this approach proves advantageous for clinicians in making medical decisions regarding single nucleotide variants, it has not yet been applied to deletions or insertions(Alay et al., 2023).

CONCLUSION

In a nutshell, the interpretation of DNA variants in clinical medical genetics is a numerous and evolving procedure that requires meticulous evaluation and categorization of genetic variations. The guidelines established by the American College of Medical Genetics and Genomics (ACMG) are of paramount importance in providing a uniform structure for the interpretation of variants. The guidelines suggest that in order to ascertain the clinical significance of variants, it is advisable to incorporate various forms of evidence such as functional assays and population data. The task of deciphering the meaning of variants of unknown clinical significance (VUS) poses difficulties in both clinical settings and genetic investigations. The existence of variants of uncertain significance (VUS) underscores the disparity between our proficiency in sequencing DNA and our competence in precisely deciphering its meaning. The challenge is especially conspicuous in rare diseases, wherein individuals frequently experience a protracted diagnostic journey before obtaining a conclusive diagnosis.

Functional evidence, including DNA methylation profiling and minigene assays, has become a valuable tool for interpreting variants of uncertain significance (VUS). These methodologies offer supplementary assistance in ascertaining the pathogenicity of variants and distinguishing between pathogenic mutations and benign variants. The accuracy and clinical utility of variant interpretation can be further improved by integrating phenotype-genotype correlations and comprehensive clinical sequencing reports. The ACMG guidelines are utilized to classify variants into distinct categories, including pathogenic, likely pathogenic, VUS, likely benign, or benign, which serve as a framework for clinical decision-making and patient management. Nevertheless, there exist difficulties in the interpretation of variants that cause disruption in the splicing process and in situations where the clinical importance of the variant is ambiguous.

Effective variant interpretation necessitates collaboration and data sharing among researchers, clinicians, and geneticists. Facilitating the dissemination of knowledge, data, and methodologies has the potential to enhance the uniformity and precision of variant classification and interpretation. Furthermore, the incorporation of profound phenotyping, such as clinical synopses in databases such as Online Mendelian Inheritance in Man (OMIM), can furnish significant background for comprehending the biological consequences of genetic variations. To summarize, the

interpretation of DNA variants in clinical medical genetics is a multifaceted and dynamic area of study. The guidelines established by the American College of Medical Genetics and Genomics (ACMG) offer a uniform structure for the interpretation of variants. However, difficulties persist in the interpretation of variants of uncertain significance (VUS) and those that interfere with splicing. Sustained investigation, cooperative efforts, and progress in operational assessments and information exchange are imperative for enhancing the precision and practicality of variant interpretation in the field of medical genetics.

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INVESTIGATION OF EPIGENETICS AND GENETIC BIOMARKERS IN CANCER DIAGNOSIS: LIQUID BIOPSY

Elif ERTÜRK

- Affiliation: Bursa Uludag University, Vocational School of Health Services, Bursa/TURKIYE
- ORCID: 0000-0001-7668-796X
- Mail: eliferturk@uludag.edu.tr

INTRODUCTION

Liquid Biopsy in Cancer

Recently, liquid biopsy has emerged as a new generation and valuable approach that spreads from primary and metastatic sites with genetic profiles of cancerous lesions to the blood (Crowley et al. 2013). Because body fluids are readily available, liquid biopsy is recognized as a non-invasive and reproducible test that allows dynamic evaluation of certain molecular biomarkers, can initiate disease relapse or treatment resistance, and potentially predict treatment response and prognosis. Various nucleic acids such as tumor cells, circulating free DNA (cfDNA), circulating tumor DNA (ctDNA), microRNAs (miRNAs), non-coding RNA, microvesicles (eg exosomes), and circulating tumor cells (CTCs) releases the types. ctDNA should not be confused with cfDNA, a broader term describing DNA that is not necessarily of tumor origin. Liquid biopsies rely on these surrogate resources for rapid and cost-effective molecular characterization of tumors using minimally invasive biological matrices (Crowley et al., 2013; Massihnia et al., 2016). Many studies have shown that malignant tumors can secrete significant amounts of DNA into the bloodstream of cancer patients as ctDNA by mechanisms associated with cell death such as necrosis and apoptosis (Crowley et al. 2013) or by active secretion of exosomes (Thakur et al. 2014). Also, in ctDNA; DNA molecular signatures in tumor cells can also be detected, including gene mutations, microsatellite instability, loss of heterozygosity, copy number changes, and DNA hypermethylation (Elshimali et al., 2013; Schwarzenbach et al., 2015; Massihnia et al., 2016). The half-life of circulating ctDNA is between 16 minutes and 2.5 hours, thus allowing real-time and dynamic monitoring of tumor states (Crowley et al. 2013). ctDNA lengths are usually close to 166 base pairs, but they can be 2 or 3 times as long. It is estimated that the formation of such short fragments is due to the DNA cleavage enzymes usually cutting between two nucleosomes during cell death and the preservation of the DNA wrapped in the nucleosome (Crowley et al. 2013). In a healthy person, cfDNA is as low as 5 ng/ml; however, this amount may increase 5-10 times in cancer patients (Crowley et al. 2013).

In some aspects, the use of methylation signatures to detect fetal or cancer-associated ctDNA in plasma has certain advantages over methods based on genetic differences. Especially recently, an increasing number of studies have shown DNA methylation of ctDNA in blood; suggests it as a

very promising tumor marker in early diagnosis, risk assessment, response to treatment, minimal invasion and prognosis of breast cancer. Moreover, although the amount of ctDNA in serum may be higher than in plasma, it has been shown that plasma represents a better source of ctDNA than serum due to less risk of cell contamination and low background concentration of wild-type DNA (Li et al. 2016). Furthermore, the DNA methylation profile is highly tissue-specific, but also consistent across different individuals in certain tissue types (Rauscher et al. 2015). Application of this concept in the analysis of plasma DNA methylation data allows one to determine the tissue origin of the ctDNA (Scartozzi et al., 2011; Fan et al., 2014). This type of tissue-origin analysis allows quantification of ctDNA from tissues of interest and thus provides an approach to monitor body status in various pathological conditions. Second, compared with genetic changes, epigenetic modifications have higher consistency in cancer. In fact, any two tumors of the same type usually share very few somatic mutations (Montero et al. 2006), while epigenetic profiles are very similar given that they originate from the same tissue (Scartozzi et al., 2011; Fan et al., 2014). In clinical practice, informative DNA methylation biomarkers can be extracted from solid tumors or plasma DNA of cancer patients. Meanwhile, given the high heterogeneity of tumors, some studies are investigating biomarkers from relevant normal tissues rather than tumors. For example, Gai et al. (2018) discovered liver and colon-specific DNA methylation biomarkers by examining the methylation of normal liver and colon tissues. They also used these experiments to differentiate patients with hepatocellular carcinoma and colorectal cancer from healthy subjects. Therefore, Gai et al. (2018) suggested that tissue-specific biomarkers for plasma DNA-based cancer testing are reasonably consistent among cancer patients. These studies showed that a more general method could be developed by targeting informative DNA methylation biomarkers for cancer testing. Although many studies have described methylation of tumor suppressor genes in serum or plasma samples and corresponding primary breast tumors, DNA methylation was not detected in plasma or serum of healthy controls (Skvortsova et al. 2006). In pre-treatment sera of patients with breast cancer, particularly RASSF1 (known RASSF1A) and APC, are independently associated with poorer prognosis and higher relative risk for survival and are a stronger predictor than standard prognostic parameters (Jahr et al., 2001; Muller et al., 2003; Skvortsova et al., 2006).

Tumor progression is actually one of the most critical factors affecting breast cancer prognosis. Existing approaches based on a combination of radiological studies and serum protein biomarker measurements are routinely used to detect and monitor disease progression. However, the sensitivity and specificity of these tests are limited (Locker et al., 2006; Nikolaou et al., 2018; Ning et al., 2018). Emerging evidence has shown that detection of ctDNA can be a minimally invasive strategy for early prediction of tumor progression before the clinical manifestation of metastasis (Zheng et al., 2017; Wang et al., 2018). From this perspective, it has attracted great interest in recent years to identify new diagnostic, prognostic and predictive molecular biomarkers such as those tested in tumor tissue, metastases and blood circulation, and many researchers have put forward their studies in this direction (Bhangu et al., 2018; Gabriel et al., 2018).

Cancer Epigenetics and Gene Methylations

Cancer development; It is a multifactorial process that includes changes in the combination of genetic, epigenetic and environmental factors (Ogino et al. 2013). DNA methylation, one of the most extensively investigated epigenetic DNA modifications, is an important epigenetic regulatory mechanism for gene transcription activities (Rhee et al. 2013). In particular, aberrant methylation in promoter regions is now multistage. It is accepted as the earliest and most common molecular event in the process of carcinogenesis and progression to malignancy (Heyn et al. 2012). To date, accumulating evidence has confirmed the important role of abnormal DNA methylation in tumor development and recognized methylation changes of certain genes as a promising biomarker for early detection of various cancers (Noehammer et al. 2014).

Many studies have focused on ESR1 methylation in various types of cancer (Magnani et al., 2015; Sahnane et al., 2015; Kuo et al., 2016). However, only a limited number of studies prove clinical significance in diagnosis (Dou et al. 2016), prognosis (Kirn et al. 2014), and response to treatment (Sood et al. 2015). In breast cancer, silencing of the ESR1 gene due to ESR1 methylation plays an important role in protein expression, while ESR1 methylation in peripheral blood is significantly associated with a lack of ER expression in excised tumor tissue (Martínez-Gal. et al. 2014). Therefore, assessment of ESR1 methylation may add prognostic value in identifying luminal phenotypes with poor prognosis and patients with potentially greater resistance to hormonal therapy (Martínez-Gal. et al.

2014). Mastoraki et al. (2018) evaluated ESR1 methylation and paired plasma ctDNA in CTCs as a potential biomarker for response to everolimus / exemestane treatment (Mastoraki et al. 2018). A highly sensitive and specific real-time methylation-specific PCR (MSP) analysis for ESR1 methylation has been developed and includes (i) formalin-fixed paraffin-embedded (FFPE) 65 primary breast tumors, (ii) EpCAMþ CTC fractions (122 patients and 30 healthy controls), (iii) plasma ctDNA (108 patients and 30 healthy controls) and (iv) CTCs and matched plasma ctDNA of 58 breast cancer patients. ESR1 methylation status was investigated in CTCs isolated from serial peripheral blood samples of 19 patients with ER-positive/HER2-negative advanced breast cancer receiving everolimus/exemestane. Accordingly, ESR1 methylation: (i) in FFPE: 25/65 (38.5%), (ii) EpCAMþ CTC fractions: 26/112 (23.3%) patients and healthy controls 1/30 (3.3%) and (iii) in plasma ctDNA: 8/108 (7.4%) patients and 1/30 (3.3%) healthy controls were detected. In addition, ESR1 methylation status was determined to be highly concordant in CTCs and 58 paired DNA samples isolated from the corresponding plasma. In the study, it was revealed that ESR1 methylation in CTCs is associated with a lack of response to everolimus / exemestane treatment, and ESR1 methylation can also be evaluated as a potential liquid biopsy-based biomarker (Mastoraki et al. 2018). In addition, the same researchers in different studies, RASSF1A methylation in ctDNA of ovarian cancer patients (Giannopoulou et al. 2017), CST6 (Chimonidou et al. 2013), SOX17 (Chimonidou et al. 2013) and BRMS1 (Balgkouranidou et al. 2014) methylation in breast cancer cases and non-small cell lung cancer (NSCLC) reported SOX17 methylation in their patients (Balgkouranidou et al. 2016).

Many studies have reported that multiple cancer-related genes can offer diagnostic information for breast cancer. In another study evaluating methylation levels of six candidate genes (EGFR, GREM1, PDGFRB, PPM1E, SOX17 and WRN) as biomarkers for early detection of breast cancer, quantitative analysis of the promoter methylation of these genes was performed from 86 breast cancer patients and 67 healthy controls. It was determined that EGFR, PPM1E and 8 gene-specific CpG islets showed significant hypermethylation in the plasma of cancer patients and were significantly associated with breast cancer. As a result of the study, it was stated that the combinations of multiple hypermethylated genes or CpG regions significantly improved the predictive performance for the detection of breast cancer (Zibo et al. 2016). In a different study, we investigated

whether SOX17 promoter methylation was related to the methylation pattern in CTCs and cfDNA isolated from plasma of breast cancer patients. SOX17 methylation in 79 primary breast tumors, 114 paired DNA samples isolated from CTC and cfDNA, and 60 healthy individuals evaluated. The SOX17 promoter was found to be methylated in 68 (86.0%) of 79 primary breast tumors. In addition, in CTCs, SOX17 is methylated in 19 (34.5%) of 55 patients with early breast cancer, 27 (45.8%) of 59 patients with metastatic cancer, and 1 (4.3%) of 23 healthy individuals, whereas SOX17 in paired cfDNA, methylated in 1 of 49 (2.0%), 24 (40.7%) of 59 and 19 (34.5%) of 55 of the same groups, respectively. In addition, a significant correlation was found between cfDNA and CTCs for SOX17 methylation in patients with early breast cancer (p=0.008), but not in patients with confirmed metastases (p=0.283). In the study, the SOX17 promoter was found to be highly methylated in primary breast tumors, CTCs isolated from breast cancer patients, and corresponding cfDNA samples. However, the findings show a direct link between CTCs and cfDNA in patients with operable breast cancer after surgical removal of the primary tumor (Zibo et al. 2016).

Cancer Genetics and Somatic Mutations

All cancers arise as a result of changes in the DNA sequence (Stratton et al. 2009). With the development and widespread use of new DNA sequencing technologies in the last quarter century, a comprehensive knowledge has emerged about these mutations (Stratton et al. 2009). In breast cancer, it is known that the presence of germline mutations in BRCA genes increases the risk of developing breast cancer 5 times in individuals with these mutations (Kuchenbaecker et al. 2017). It is stated that the prevalence of BRCA1 and BRCA2 mutations in individuals at high risk for breast cancer in the Turkish population is approximately 19% (Geredeli et al. 2019). Although BRCA genes are important genes that should be mentioned in breast cancer, the most common gene mutations in breast cancer are somatic mutations that occur in many different genes during the tumorigenesis process. When all breast cancer patients are evaluated, it can be mentioned that there are a wide variety of mutations in hundreds of different genes (copy number change, point mutation, insertion-deletion, etc.). (Berger et al., 2018; Ciriello et al., 2015). In the light of recent large-scale studies, it is now known which gene mutations are encountered and how often (Berger et al., 2018; Ciriello et al., 2015). CDH1, PIK3CA, PTEN and RUNX1 mutations are the most common mutations in invasive lobular breast carcinomas (Ciriello et al. 2015). In invasive ductal breast carcinomas,

there are point mutations in the TP53, PIK3CA, MAP3K1, MAP2K4, GATA3, MLL3, CDH1 genes and truncation mutations that form the stop codon; Copy number changes are observed in PIK3CA, ERBB2, TP53, MLL3, MAP2K4, CDKN2A, PTEN and RB1 genes (Cancer Genome Atlas Network 2012). The presence of mutations in some of these genes directly affects drug selection in treatment, while mutations in some other genes, such as TP53, provide information about prognosis and survival (Børresen et al. 1995).

Mutations to be studied by DNA sequencing methods are traditionally obtained from FFPE patient samples. In addition to this methodology, the potential for clinical use of liquid biopsy specimens has been increasingly explored in recent years. Especially in recent years, various subjects such as treatment follow-up, response, recurrence, and residual disease follow-up have been focused on (Liang et al., 2016; Garcia-Murillas et al., 2019; McDonald et al., 2019; Butler et al., 2019). The hypothesis put forward in studies on treatment follow-up is based on the change in the mutation frequency detected in breast cancer patients during the treatment process (Garcia-Murillas et al. 2019). According to this hypothesis, an increase in a certain mutation frequency in the next test is associated with the progression of the disease (Liang et al. 2016). In a study conducted with whole exome sequencing (WES) data of tumor tissue, blood was drawn at certain intervals with panels containing 16 mutations in each patient individual, and the frequency changes of these mutations (variant allele frequency, VAF) were followed for 4 years. And it has been shown that the increase in VAF in relapsed patients may herald relapse until about 2 years ago (Coombes et al. 2019). In a similar study in which individual mutations were followed, it was stated that molecular relapse could occur an average of 10.7 months before clinical relapse. In this sense, it has been argued that molecular relapse may have clinical validity (Garcia-Murillas et al. 2019). In another study using WES data, researchers stated that they were able to capture variants with a high sensitivity (0.01%) by developing a special ctDNA capture panel containing 20-50 patient-specific mutations (Butler et al. 2019). In this study, it was concluded that varying variant allele frequencies may be a marker of tumor growth (Butler et al. 2019). In another study, next-generation sequencing (NGS) was performed with a panel of 82 genes in germline, tumor and plasma DNA samples of breast cancer patients receiving neoadjuvant chemotherapy (NAC) (Kim et al. 2017). In the diagnosis of the disease, it was observed that the frequency change of the

variants detected in the NAC and the samples taken during the operation was correlated with the residual tumor burden observed during the operation (Kim et al. 2017).

CONCLUSION

In conclusion, it is well known that both genetic and epigenetic changes play an important role in the initiation and progression of carcinogenesis in breast tissue and that they can be recognized in the cfDNA of cancer patients (Gallardo-Gomez et al., 2018). Recently completed clinical trials have been published showing that cfDNA reflects recurrence, treatment response, or survival in other breast cancer patients receiving triple-negative or neoadjuvant chemotherapy (Magbanua et al., 2020; Radovich et al., 2020). These developments indicate that cfDNA samples obtained from breast cancer patients may soon be used in routine clinical use to determine diagnosis, prognosis, treatment follow-up or response. In this context, the clinical utility of cfDNA analysis can be investigated in cancer patients by evaluating the DNA methylation status and determining the changes in the mutation level. In addition, molecular biomarkers that are prognostic and/or predictive of treatment follow-up and response can be identified.

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IMMUNOTHERAPY IN CANCER TREATMENT

Hayrani Eren BOSTANCI

- Affiliation: Department of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University Sivas/TURKIYE
- ORCID: 0000-0001-8511-2316
- Mail: erenbostanci@hotmail.com

Faruk Kaan ÇELİK

- Affiliation: Yıldız Technical University, Faculty of Arts and Sciences, Department of Molecular Biology and Genetics İstanbul/TURKIYE
- ORCID: 0009-0004-0565-764X
- Mail: farukkaancelik1@gmail.com

İnci TEMUR

- Affiliation: Yıldız Technical University, Faculty of Arts and Sciences, Department of Molecular Biology and Genetics Istanbul/TURKIYE
- ORCID: 0009-0001-1144-8551
- Mail: incitemur@gmail.com

INTRODUCTION

Cancer, which causes the death of approximately 10 million people every year, is a type of disease that begins to spread to other parts of the body by uncontrolled proliferation of cells in the tissues and organs of our body. There are more than 100 types of cancer diagnosed. Cancer types are named according to the tissue or organ in which they occur. The most known and generally preferred cancer treatment methods are surgery, radiotherapy and chemotherapy. However, when the studies conducted in recent years are examined, it is seen that immunotherapeutic treatment methods also show promise (Hamilton, 2010). In this section, many topics such as the emergence of immunotherapy, different application methods, advantages, disadvantages and the future of immunotherapy are mentioned.

Transformation of a Normal Cell into Cancer

Cancer types develop from our cells, the smallest unit of life in the body. In order to understand the nature of cancer, we must first know how the structure of cells deteriorates and becomes cancerous. Cells have limited ability to divide, they cannot divide indefinitely. For a healthy cell to divide, it must be stimulated by signals. While dividing, when a healthy cell encounters another cell, it ends dividing, this is called contact inhibition. When cells get old and damaged, they are programmed to die in a controlled manner. The programmed death of the cell is called apoptosis. (Gerard, 2014).

For various reasons, sometimes cells continue to divide without the need for new cells. At the center of cells is the nucleus, which contains DNA, our genetic material specific to the living thing. DNA plays the biggest role in the cell and organism's vital functions. Cancerous cells can arise from damage to DNA. If DNA damage occurs in the normal life cycle of a cell, the cell tries to heal itself or kills itself through various pathways. Since the damaged DNA in cancer cells is not repaired, the cell begins to multiply uncontrollably. DNA can be damaged due to environmental and genetic factors. Cancer cells that accumulate as a result of this uncontrolled proliferation are called tumors (Bernstein, 2013).

Tumors are classified as benign and malignant in the literature.

Benign tumors are not cancerous. They do not spread to other parts of the body. These are often surgically removed and often do not recur.

Malignant tumors are cancerous tissues. The cells in these tumors are very different from normal cells in terms of cellular structure and genetic information compared to healthy cells. They divide randomly in an uncontrolled way and have the ability to infiltrate by compressing the tissues they are in. If they infiltrate the tissue, they can cause great damage. Cancer cells can break away from the tumor they formed by infiltrating the blood or lymph circulation and spread to other parts of the body. After entering the circulation, they can form tumor colonies in random places and continue to grow. The random spread of cancer to other parts of the body through the circulation is called metastasis. Cancer that spreads to a different part of the body as a result of metastasis is called metastatic cancer. For example, breast cancer that causes cancer in the lung is called metastatic breast cancer. (Pierce, 1971)

Diagnosis

Early diagnosis of cancer is as vital as its treatment. Cancer is a disease that can manifest itself with more than one symptom. There are prominent symptoms such as chest stiffness, headaches, skin changes and eating problems. Often these symptoms are not caused by cancer, but by benign tumors or other health problems. If there are symptoms that last for a few weeks, a doctor should be consulted and tests should be done without wasting time. If cancer is diagnosed, the doctor will order another set of tests or procedures to determine the stage of the cancer.

The stage of the cancer refers to its grade and indicates how big the tumor is and whether it has spread. Once the doctor finds out the stage of the cancer, he or she can recommend treatment and discuss the prognosis. Thus, the most appropriate treatment method can be started (Hamilton, 2010).

Types Of Cancer Treatments

There are many types of cancer treatments. What the treatment will be is decided together with the doctor as a result of the stage of the cancer of the person. The most known and used cancer treatment methods are surgery, radiotherapy and chemotherapy according to the stage of the cancer. Immunotherapy, which is one of the cancer treatment methods, has a very important place today.

Immunotherapy is a type of cancer treatment that helps your body fight infections and cancer by stimulating or suppressing our immune system in various ways. Our immune system consists of white blood cells and organs

and tissues of the lymphatic system. Some types of immunotherapy target only certain cells of the immune system. Others affect the immune system in a general way. Immunotherapy is a biological therapy. The treatment method that uses substances made from living organisms in cancer treatment studies is called biological therapy (Roy, 2016; Esfahani, 2020).

The Emergence of Immunotherapy

Immunotherapy is a type of cancer treatment that uses the body's own immune system to fight cancer cells. It is an area that has been studied and studied for more than a century, and significant developments have been made in this area in recent years. The discovery of immunotherapy was revealed by the work of scientists such as William Coley and Paul Ehrlich towards the end of the 19th century (Dobosz P, Dzieciątkowski T.,2020).

William Coley is an American surgeon and is also considered one of the pioneers of cancer immunotherapy. Coley observed that some cancer patients who experienced bacterial infections in the late 1800s also had tumor regression. As a result of this observation, Coley tried to create an immune response against tumors by injecting cancer patients into the body with bacterial components, now known as Coley toxins. Paul Ehrlich, a German scientist, made important contributions to immunotherapy in the early 20th century. He developed the concept of immunological specificity, arguing that the immune system can selectively recognize and attack certain foreign substances, including cancer cells. Ehrlich's work laid the foundation for the development of targeted therapies (Dobosz P, Dzieciątkowski T.,2020).

In recent years, significant advances have been made in the field of immunotherapy, which has led to breakthrough treatments and therapies. An important breakthrough was the discovery of immune checkpoint inhibitors, which revolutionized cancer treatment. The role of immune checkpoints and suppressing the immune response against cancer cells was discovered by James P. Allison and Tasuku Honjo, who were jointly awarded the Nobel Prize in Physiology or Medicine in 2018. American immunologist James P. Allison and a Japanese immunologist Tasuku Honjo independently identified immune checkpoints such as CTLA-4 and PD-1 and their inhibitory effects on immune responses. Their discoveries paved the way for the development of immune checkpoint inhibitors that have shown remarkable efficacy in the treatment of various types of cancer.

Since then, numerous researchers and pharmaceutical companies have contributed to the advancement of immunotherapy. Ongoing research continues to improve our understanding of the immune system and develop new immunotherapeutic approaches. Collaboration between scientists, clinicians and pharmaceutical companies plays a vital role in the discovery, development and improvement of immunotherapy treatments.

It is important to note that the field of immunotherapy is very broad and many scientists and researchers have made valuable contributions to the development of this field. The individuals mentioned here represent several key figures who have played important roles in advancing the field. (Dobosz et al.,2020)

Immunotherapy Treatments

Immunotherapy involves various pathways and mechanisms that interact with the immune system to recognize and eliminate cancer cells.

Here are some of the major immunotherapy avenues, with their associated details:

Immune Checkpoint Inhibitors:

The immune system has a set of checkpoints that help regulate its response to infection and illness. Immune checkpoints are located on T cells and play a crucial role in regulating the immune response. Normally, immune checkpoint inhibitors prevent overactivation of the immune system and prevent healthy cells from being attacked. These checkpoints can be hijacked by cancer cells, allowing them to evade the immune system and grow uncontrollably.

Immune checkpoint inhibitors are a new class of drugs that target these checkpoints and help the immune system recognize and attack cancer cells. There are two main types of immune checkpoint inhibitors: CTLA-4 inhibitors and PD-1/PD-L1 inhibitors. CTLA-4 inhibitors work by blocking the CTLA-4 protein, which helps prevent T cells from being activated. PD-1/PD-L1 inhibitors work by blocking the PD-1 and PD-L1 proteins, which help prevent T cells from killing cancer cells. Immune checkpoint inhibitors have been shown to be effective in treating a variety of cancers, including melanoma, lung cancer, and kidney cancer. It has also been shown to prolong survival in patients with advanced cancer. However, immune checkpoint inhibitors can also cause side effects such as inflammation and organ damage.

Immune checkpoint inhibitors are a promising new treatment for cancer (Dolladille et al., 2020).

However, the use of immune checkpoint inhibitors presents challenges. Some patients may experience immune-related adverse events (irAEs) as a result of increased immune response. These are symptoms that range from mild to severe and can affect different organs, requiring close monitoring and appropriate management. In addition, not all patients respond equally to immune checkpoint inhibitors, requiring widespread use and better understanding of the use of predictive biomarkers to identify those most likely to benefit from these treatments.

In conclusion, immune checkpoint inhibitors such as CTLA-4, PD-1 and PD-L1 inhibitors have revolutionized cancer treatment. By blocking the inhibitory signals transmitted from these checkpoints, it increases the potential of the immune system to target and eliminate cancer cells. Research and advances in this area hold great promise for healing patients and bringing us closer to more effective personalized cancer immunotherapy (Naimi et al., 2022).

CAR-T Cell Therapy Pathway:

T cells are a type of white blood cell that is part of the body's immune system. They help fight infection by recognizing and killing harmful cells such as cancer cells. CAR-T cell therapy is a type of immunotherapy that uses genetically modified T cells to target and kill cancer cells. It works by designing a protein designed to recognize a specific antigen on cancer cells by expressing a chimeric antigen receptor (CAR) on a patient's own T cells. When CAR binds to the antigen, it sends a signal to the T cell that activates it, causing it to kill the cancer cell.

The CAR-T cell therapy process is complex and includes several steps. First, T cells are collected from a patient's blood. The T cells are then sent to a lab where they are genetically engineered to express CAR. The engineered T cells are then grown in the laboratory until they reach sufficient numbers. The cells are then given back to the patient, where they can target and kill the cancer cells.

It has been used to treat a variety of blood cancers, including leukemia, lymphoma, and myeloma. It has also been used to treat certain solid tumors such as glioblastoma. Although it is a relatively new treatment, it shows great promise in cancer treatment. However, CAR-T cell therapy is not

without risks. Some patients may experience side effects such as cytokine release syndrome (CRS) or neurotoxicity. CRS is a serious side effect that can occur when CAR-T cells begin to attack cancer cells. CRS can cause fever, inflammation, and organ damage. Neurotoxicity is a side effect that can affect the brain and nervous system. Neurotoxicity can cause symptoms such as headache, confusion, and seizures.

Despite the risks, CAR-T cell therapy is a promising new treatment for cancer. It has the potential to be a very effective treatment for cancer and is being studied for use in the treatment of a wider range of cancers (Tang et al., 2022).

Monoclonal Antibody Pathway:

Monoclonal antibodies (mAbs) have emerged as a promising avenue in targeted cancer therapy trials. mAbs are white blood cells designed in vitro to bind to specific proteins on the surface of cancer cells. These lab-engineered white blood cells specifically bind to proteins on the surface of cancer cells and mark them, and they can directly inhibit the growth of cancerous cells, trigger immune responses against cancer cells, or deliver cytotoxic agents to the tumor site. Binding of mAbs (Monoclonal antibodies) to tumor-associated antigens can activate immune cells such as natural killer (NK) cells and macrophages to destroy cancer cells through antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). After binding to tumor-associated antigens, mAbs trigger the activation of complement proteins. This activation results in the formation of a membrane attack complex that punctures cancer cells and leads to their death. This complementary pathway adds another layer of defense against cancer cells, further increasing the therapeutic potential of monoclonal antibodies.

Beyond their immunological functions, monoclonal antibodies can be engineered to serve as carriers for potent cytotoxic agents. By conjugating these cytotoxic payloads to mAbs, scientists can deliver them precisely to the tumor microenvironment, minimizing systemic toxicity and maximizing therapeutic effect. This targeted delivery approach represents a significant advance in cancer therapy as it increases the efficacy of cytotoxic agents while reducing adverse side effects on healthy tissues.

In conclusion, the pathway of monoclonal antibodies in targeted cancer therapy is a fascinating endeavor involving direct inhibition of cancer cell growth, triggering of immune responses, and activation of immune

effector cells for antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Through these various mechanisms, monoclonal antibodies provide a personalized and precise approach to fighting cancer. As our understanding of this graceful pathway continues to deepen, the therapeutic potential of monoclonal antibodies expands, promising to revolutionize the field of cancer therapy and improve patient outcomes (Lu et al., 2022).

Cancer Vaccine Path

Cancer vaccines are designed to stimulate the immune system to recognize and attack cancer cells. Unlike traditional vaccines applied to prevent diseases, it is administered to people diagnosed with cancer.

There are 3 main types of cancer vaccines:

Cancer-specific antigen vaccines: These vaccines contain antigens specific to cancer cells or the genetic material (DNA or RNA) that encodes these antigens. This type of vaccine is specific to certain types of cancer and can train the immune system to specifically recognize and attack these cancer cells.

Tumor-associated antigen vaccines: These vaccines can be developed using tumor-associated antigens commonly found in individuals with a certain type of cancer and include antigens commonly found on cancer cells. This type of vaccine has antigens derived from tumor cells themselves and can be used to mount an immune response against cancer cells that express these specific antigens.

Dendritic cell vaccines: These vaccines are made from dendritic cells, which are immune cells that help present antigens to the immune system. Dendritic cells initiate an immune response by processing and presenting vaccine antigens to T cells. This interaction activates a variety of T cells, including cytotoxic T cells, which can identify and eliminate cancer cells that express targeted antigens. Dendritic cell vaccines can be used to train the immune system to recognize and attack cancer cells.

Cancer vaccines are still in the early stages of development, but they have shown some promise in clinical trials. For example, a vaccine called Provenge (sipuleucel-T), a dendritic cell vaccine, has been shown to prolong survival in men with advanced prostate cancer. Cancer vaccines can help train the immune system to recognize and attack cancer cells, thereby reducing the

risk of cancer recurrence, increasing the effectiveness of other cancer treatments such as chemotherapy and radiation therapy, and improving the development of cancer by training the immune system to recognize and attack cancer cells before they become cancerous. It has benefits such as prevention (Donninger et al., 2021).

Cytokine Based Immunotherapy

Cytokine-based immunotherapy encompasses a range of strategies that include the use of cytokines, BCG, and immunomodulatory drugs to modulate immune responses for therapeutic purposes. Cytokines, which are small proteins secreted by immune cells, play a vital role in regulating immune responses.

Interferons and interleukins are examples of cytokines used in immunotherapy. Interferons stimulate immune cells and have antiviral and antitumor properties, while interleukins enhance antitumor immune responses by promoting proliferation and activation of immune cells. These cytokines can be administered as recombinant proteins to enhance immune activity against cancer cells.

Another method, BCG or Bacillus Calmette-Guérin, is a weakened type of bacteria that causes tuberculosis but is harmless to humans. It is mainly used in the treatment of bladder cancer. When administered directly into the bladder through a catheter, BCG induces an immune response against cancer cells. Researchers are also investigating its potential applications in other types of cancer.

Immunomodulatory drugs represent another category of cytokine-based immunotherapy. Medications such as thalidomide, lenalidomide, and pomalidomide function by modulating the immune system. They inhibit the release of specific cytokines such as IL-2 and prevent the formation of new blood vessels in tumors. These drugs are commonly referred to as angiogenesis inhibitors because of their capacity to target tumor blood flow. Also, imiquimod, a topical cream, increases immune responses by stimulating the release of cytokines from skin cells.

Leveraging the potential of cytokines, BCG, and immunomodulatory drugs, cytokine-based immunotherapy aims to manipulate the immune system and facilitate effective immune responses against cancer. Ongoing research in this area seeks to optimize these approaches and explore their potential applications in various types of cancer.

The benefits of cytokine-based immunotherapy extend beyond its direct therapeutic effects. It may also contribute to reducing the risk of cancer recurrence by training the immune system to recognize and attack cancer cells, thereby increasing long-term outcomes. Additionally, it has the potential to increase the effectiveness of other cancer treatments such as chemotherapy and radiation therapy. Moreover, by training the immune system to identify and eliminate cancer cells before they develop into cancer, cytokine-based immunotherapy shows promise in the prevention of cancer development (Berraondo et al., 2019).

These treatment variants represent the key treatments involved in immunotherapy. Each pathway has its own unique goals and approaches, and ongoing research aims to further elucidate and optimize these pathways for effective cancer.

Advantages of Immunotherapy

Immunotherapy offers significant benefits, revolutionizing the field of cancer treatment and improving outcomes for many patients. Some of the positive aspects and advantages of immunotherapy can be explained under the following headings:

Targeted Approach: Immunotherapy uses the body's immune system to specifically recognize and attack cancer cells, offering a more targeted approach compared to traditional treatments such as chemotherapy and radiation therapy. It can mark by binding to receptor proteins on the surface of cancer cells, enhancing the immune system's natural ability to identify and eliminate cancer cells.

Long-Term Antitumor Response: Unlike some other cancer treatments, immunotherapy can elicit long-lasting responses. By training the immune system to recognize cancer cells, immunotherapy can create an immunological memory. This memory can help prevent cancer recurrence and provide continued protection against disease.

Treatment of Various Types of Cancer: Immunotherapy has shown efficacy in a number of cancer types, including melanoma, lung cancer, kidney cancer, bladder cancer, and more. It has expanded treatment options for patients who may have limited alternatives or who do not respond to conventional treatments. The versatility of immunotherapy has made it a valuable tool in the fight against cancer.

Combination Therapies Potential: Immunotherapy can be combined with other treatment modalities such as chemotherapy, radiation therapy, targeted therapy, or other immunotherapies. This synergistic approach can increase treatment efficacy and lead to better outcomes. Combination therapies are being actively explored in ongoing research and offer promising prospects for improved patient responses.

Reduced Systemic Toxicity: Immunotherapy usually has fewer side effects compared to traditional cancer treatments such as chemotherapy. This is because immunotherapy is designed to selectively target cancer cells while minimizing damage to healthy cells. By exploiting the body's immune system, immunotherapy can reduce the systemic toxicity and associated adverse effects commonly seen in conventional therapies.

Potential for Personalization: Immunotherapy shows promise for personalized medicine approaches. Researchers are working on biomarkers and genetic profiling to identify patients more likely to respond positively to immunotherapy. This can help tailor treatment plans and improve patient outcomes by selecting the most appropriate treatments for individual patients.

Extended Survival Rates: Immunotherapy has shown impressive results in prolonging overall survival in some cancer patients. In certain cases, patients who previously had limited treatment options or poor prognoses experienced significant improvements in survival and quality of life with the help of immunotherapy.

It is important to note that the effectiveness of immunotherapy may vary depending on individual factors such as cancer type, stage, and patient-specific characteristics. Consulting healthcare professionals and evaluating individualized treatment plans is crucial to determine the best course of action for each patient (Tan S, Li D, Zhu X.,2020).

Overall, immunotherapy offers a promising avenue for cancer treatment by harnessing the power of the immune system to fight cancer, providing new hope and improved outcomes for patients.

Side effects in immunotherapy treatments

Side effects of immunotherapy can vary depending on the type of immunotherapy, the patient, and the specific cancer being treated. It is important to note that not all patients will experience side effects, or that for those who do, the severity can range from mild to more pronounced.

Some of the most common side effects of immunotherapy include:

Immune-related adverse events (irAEs): irAEs are side effects caused by the body's immune system overreacting to treatment. IRAEs can affect any part of the body, but are most common in the skin, gastrointestinal tract, liver, and lungs.

Infections: Immunotherapy can weaken the immune system, making it harder for the body to fight infections.

Autoimmune diseases: Immunotherapy can sometimes trigger autoimmune diseases, which are conditions in which the body's immune system attacks healthy cells.

Fatigue is a common side effect and can range from mild fatigue to more severe fatigue. This may be accompanied by a lack of energy and decreased motivation. Immunotherapy can cause skin-related side effects such as redness, itching, dryness or blistering. In some cases, more severe skin reactions such as dermatitis or psoriasis may occur.

Immunotherapy can cause gastrointestinal side effects such as nausea, vomiting, diarrhoea, constipation, loss of appetite or stomach pain. Some patients may experience flu-like symptoms such as fever, chills, muscle aches, joint pain, headache or general malaise. Immunotherapy may cause coughing, shortness of breath, wheezing, or other respiratory symptoms.

Some immunotherapies can affect the endocrine system, leading to hormonal imbalances and causing symptoms such as thyroid dysfunction or adrenal insufficiency. In rare cases, immunotherapy may affect liver and kidney function, causing abnormal blood test results or other organ-related side effects. Although not common, allergic reactions to immunotherapy can occur and range from mild to severe. Signs of an allergic reaction may include hives, itching, swelling, difficulty breathing or a fast heartbeat.

It is very important for patients to immediately report any side effects they experience to their healthcare team. Many side effects can be managed with medications or supportive care, and early intervention can help minimize their impact on a patient's quality of life. In some cases, treatment may need to be temporarily stopped or adjusted to effectively manage side effects. Because immunotherapy has shown significant efficacy in the treatment of various types of cancer, it is important to remember that the potential benefits of immunotherapy often outweigh the risks of side effects (Rahman et al., 2022; Tan et al., 2020).

The Future of Immunotherapy

The future of immunotherapy in cancer treatment holds great promise. Ongoing research and advances continue to shape the field, providing exciting possibilities to further improve outcomes for cancer patients (Zhu et al., 2021; Tan et al., 2020). The areas where immunotherapy is developing can be mentioned as follows:

Precision Drug and Biomarker Discovery: By identifying specific biomarkers that predict a patient's response to immunotherapy and the development of genetic profiling, researchers can develop personalized treatment plans that maximize efficacy and minimize unnecessary treatments. Some of the most promising biomarkers for immunotherapy include:

Tumor mutation load (TMB): TMB is a measure of the number of mutations in a tumor. High TMB tumors are more likely to respond to immunotherapy.

PD-L1 expression: PD-L1 is a protein that helps cancer cells evade the immune system. High PD-L1 expression is also associated with a better response to immunotherapy.

Cancer genetics: A tumor's genetic makeup can also affect its response to immunotherapy. For example, tumors with certain genetic mutations are more likely to respond to checkpoint inhibitors.

Ongoing research is focused on discovering new biomarkers and improving existing ones. As our understanding of the immune system and cancer biology continues to advance, we can expect the development of even more personalized and targeted immunotherapies. These advances have the potential to improve treatment outcomes and bring us closer to the goal of achieving effective immune-based therapies for a wider range of cancers (Spencer et al., 2016).

Combination Therapies: Combination approaches involving different immunotherapies as well as combining immunotherapy with other treatment modalities such as chemotherapy or targeted therapy show great promise. This approach is being explored as a way to increase the efficacy and durability of immunotherapy and expand the range of cancers that may benefit from immunotherapy.

There are several different ways to combine immunotherapies. One approach is to use two or more different immune checkpoint inhibitors

together. This approach has been shown to be effective in some patients with melanoma and lung cancer. Another approach is to combine an immune checkpoint inhibitor with a targeted therapy. This approach has been shown to be effective in some patients with colorectal cancer and head and neck cancer.

Combination immunotherapy is still in its early stages of development, but has the potential to revolutionize cancer treatment. By combining different immunotherapies, researchers can create more effective and permanent treatments for a wider range of cancers.

Combination immunotherapy is a promising new approach in cancer treatment. However, it is important to note that this approach is still in its early stages of development. More research is needed to determine the optimal combinations of immunotherapies and to understand the long-term side effects of this therapy (Khalil et al.,2016).

Overcoming Resistance: Resistance to immunotherapy is a challenge that researchers are actively addressing. Some patients develop resistance to immunotherapy, which means the treatment no longer works. This is a major challenge that researchers are working to overcome.

There are a number of different mechanisms that can lead to resistance to immunotherapy. One mechanism is that cancer cells can mutate by changing the proteins targeted by immunotherapy on their surface. Another mechanism is that cancer cells can produce proteins that suppress the immune system.

Researchers are working to develop strategies to overcome resistance to immunotherapy. One strategy is the use of combination immunotherapy, which involves using two or more different immunotherapies together. Another strategy is to develop new immunotherapies that target different proteins on cancer cells.

In addition to overcoming resistance, researchers are working to develop treatments that can prevent cancer from recurring after successful immunotherapy. This is important because even if the immunotherapy is initially successful, cancer cells can sometimes start to grow back.

Researchers hope that by understanding the mechanisms of resistance to immunotherapy and developing new strategies to overcome it, they can make immunotherapy a more effective and durable treatment for cancer (Schultz et al., 2019).

New Immunotherapies and Targets: Researchers are constantly developing new immunotherapies and identifying new targets for immune system modulation. This includes research on different immune checkpoint inhibitors, adoptive cell therapies, cancer vaccines, and immunostimulating agents. Researchers are also investigating new targets in the tumor microenvironment and exploring the potential to manipulate the microbiome to increase immunotherapy efficacy. The development of new immunotherapies and identifying new targets for immune system modulation is an active area of research. These new approaches have the potential to revolutionize cancer treatment and improve patient outcomes.

Some of the most promising new immunotherapies and targets are:

New immune checkpoint inhibitors: Researchers are developing new immune checkpoint inhibitors that target different proteins on cancer cells. These new inhibitors may be more effective than existing checkpoint inhibitors and may also be effective against cancers resistant to existing checkpoint inhibitors.

Adoptive cell therapies: Adoptive cell therapies involve collecting a patient's own immune cells, designing them to be more effective at killing cancer cells, and then reintroducing them to the patient. Adoptive cell therapies have been shown to be effective in some patients with leukemia and lymphoma and are being investigated as a treatment for other cancers.

Cancer vaccines: Cancer vaccines are designed to train the immune system to recognize and attack cancer cells. Cancer vaccines have been shown to be effective in some patients with melanoma and head and neck cancer, and are being investigated as a treatment for other cancers.

Immunostimulating substances: Immunostimulating substances are substances that strengthen the immune system. Immunostimulating agents have been shown to be effective in some patients with cancer and are being investigated as a way to increase the effectiveness of other immunotherapies.

Researchers are also discovering new targets in the tumor microenvironment. The tumor microenvironment is the environment that surrounds cancer cells. It includes other cells, such as tumor-associated macrophages, as well as proteins and other molecules. The tumor microenvironment can help cancer cells grow and spread.

Researchers are exploring ways to manipulate the microbiome to make immunotherapy more supportive. The microbiome is the collection of

bacteria and other microbes that live in the body. The microbiome may affect the immune system and play a role in cancer development and progression. The development of new immunotherapies and identification of new targets for immune system modulation is an active area of research (Puhr et al., 2019).

Improved Safety Profiles: Immunotherapy can cause cancer treatment side effects as well. These side effects can be mild or severe and differ from person to person. Efforts are being made to improve immunotherapy approaches to reduce side effects and improve safety profiles. The development of enhanced safety profiles in immunotherapy is an active area of research. These new approaches have the potential to make immunotherapy a more effective and tolerable treatment for cancer patients.

This includes developing strategies to reduce immune-related side effects and finding ways to improve treatment tolerability for a wider range of patients. Some of the strategies the researchers discovered include:

Personalized immunotherapy: Personalized immunotherapy involves tailoring treatment to the patient's individual tumor and immune system. This can help reduce the risk of side effects.

Combination immunotherapy: Combination immunotherapy involves using two or more immunotherapies together. This can help increase the effectiveness of treatment while reducing the risk of side effects.

Immune checkpoint blocking inhibitors: Immune checkpoint blocking inhibitors are a type of immunotherapy that works by blocking proteins on immune cells that help cancer cells escape the immune system. Researchers are developing new immune checkpoint blocking inhibitors that may be more effective and have fewer side effects than existing inhibitors (Passalacqua et al., 2006)

Pediatric Immunotherapy:

The application of immunotherapy in pediatric cancers is an active area of research. Researchers are working to develop immunotherapies specifically designed for pediatric patients, addressing unique challenges and optimizing treatment strategies for childhood cancers.

One of the challenges of using immunotherapy in pediatric patients is that it is likely to cause irAEs in pediatric patients and is generally more aggressive in pediatric patients than adult cancers. This means that pediatric patients may need to be treated with higher doses of immunotherapy, which

can increase the risk of side effects. Researchers are working to develop more effective immunotherapies without increasing the risk of side effects in pediatric patients.

Despite the challenges, there is hope that immunotherapy will be a successful treatment for pediatric cancers. Researchers are making progress in developing immunotherapies designed specifically for pediatric patients. As this research continues, there is hope that immunotherapy will offer a new and effective treatment option for children with cancer (Wedekind et al.,2018).

Access and Affordability:

The future of immunotherapy also includes efforts to improve access and affordability for patients. Immunotherapies are often expensive and may not be covered by insurance. This can make it difficult for patients to afford this treatment.

There are several ways to improve access and affordability of immunotherapy. One way is to develop cost-effective approaches to manufacture and distribute these drugs. Another way is to explore alternative delivery methods, such as oral or inhaled treatments. These methods may be less expensive than traditional intravenous therapy.

Researchers are also working to develop generic versions of immunotherapy drugs. Generic drugs are typically much cheaper than brand-name drugs. Once generic versions of immunotherapy drugs are available, they will make this treatment more affordable for patients.

As research continues, there is hope that immunotherapy will become more accessible and affordable for patients. This will enable more patients to benefit from this promising new treatment (Ashley et al., 2020).

CONCLUSION

In conclusion, it is important to note that the field of immunotherapy is characterized by dynamic and ongoing research and development. Scientists and clinicians are working with immunotherapy in the treatment of cancer to improve treatments, increase the efficacy and safety of existing immunotherapies, and make immunotherapies more accessible and cost-effective for patients. The future of immunotherapy in cancer treatment will undoubtedly witness continued evolution as we ultimately work to improve outcomes for patients. Continual efforts to optimize immunotherapy approaches and the pursuit of groundbreaking discoveries will shape the future

of cancer treatment and offer patients new hope and possibilities in their fight against cancer.

The future of immunotherapy is bright, and as research continues, it is hoped that immunotherapy will become a standard treatment for cancer and help improve the lives of millions of patients.

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CHRONIC VENOUS INSUFFICIENCY AND PHYSIOTHERAPY

Sıla ÇELİK

- Affiliation: Uskudar University Institute of Health Sciences, Department of Physiotherapy and Rehabilitation, Istanbul/TURKIYE
- ORCID: 0000-0003-4485-8052
- Mail: sila.celik@st.uskudar.edu.tr

Ömer ŞEVGİN

- Affiliation: Uskudar University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Istanbul/TURKIYE
- ORCID: 0000-0003-2145-5939
- Mail: omer.sevgin@uskudar.edu.tr

1. Chronic Venous Insufficiency

Chronic venous disorder is a term that includes all morphological and functional abnormalities affecting the venous system, regardless of whether they produce symptoms (Eklof et al.,2009). The disease can be seen in a wide spectrum, from asymptomatic cases to patients who may form stasulcers. The most common symptoms are pain, swelling, cramps, burning, itching, tingling sensations that increase with standing still. In advanced cases, it may cause loss of time and energy by preventing daily activities (Nael& Rathbun, 2009).

2. Anatomy of Chronic Venous Insufficiency

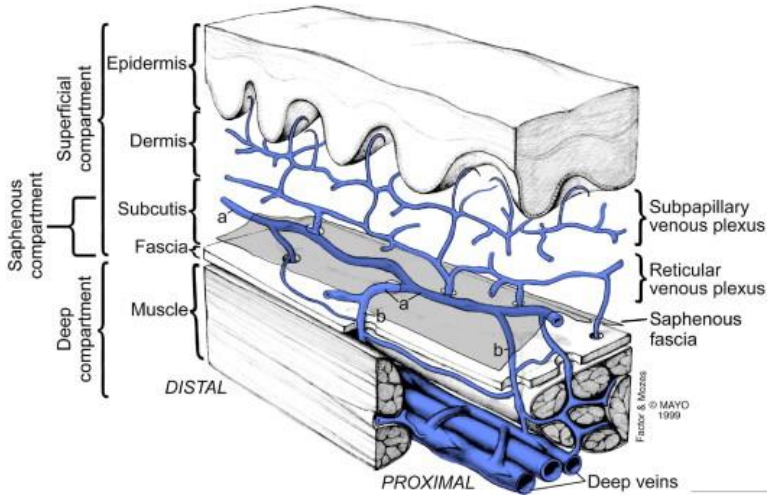

Figure 1. Relationship between the fascia and veins of the lower extremity. The fascia covers the muscle and separates the deep from the superficial compartment. Superficial veins (a) drain the subpapillary and reticular venous plexuses and they are connected to deep veins through perforating veins (b). The saphenous fascia invests the saphenous vein. The saphenous compartment is a subcompartment of the superficial compartment. From Mozes G, Gloviczki P. New discoveries in anatomy and new terminology of leg veins: clinical implications. Vasc Endovasc Surg 2004;38:367-374

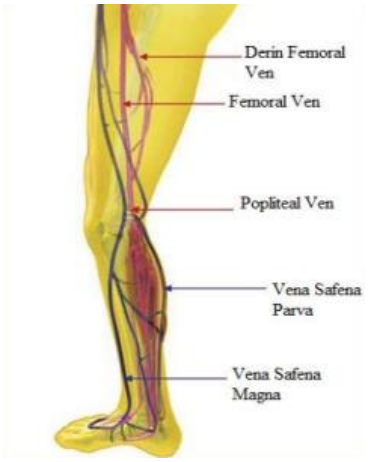

Figure 2. Deep and superficial veins of the lower extremities. (Duman 2011).

2.1 Superficial Venous System

The main superficial veins, the vena saphana magna and vena saphana parva, are located in the subcutaneous tissue under the skin, on the deep fascia surrounding the legs. The vena saphana magna ascends in the dorsum of the foot, starting from the medial superficial veins, passing in front of the medial border of the tibia and the medial malleoli. The vena saphana parva begins posterior to the lower extremity and ascends in the popliteal fascia. The longest vein of our body is the vena saphana magna (Yıldırım, 2007; Bergan & Pascarella2007; Erbil et al., 2007).

2.2 Deep Venous System

The deep vein system has low pressure, high volume and accounts for an average of 90% of the venous blood flow of the lower extremity. Deep veins supported by muscle and fascia have thinner walls compared to superficial veins. Deeply located veins can be found in our body in two ways: intramuscularly and intermuscularly. Intermuscular veins are more important than intramuscular veins in the development of chronic venous insufficiency. Except for the distal side of the intramuscular veins, all deep veins travel together with their corresponding arteries (Trayes et al. 2013). The deep venous arch alone drains venous blood from the foot and metatarsals with strong anastomoses. Beginning as the posterior tibial vein behind the medial ankle, the deep plantar venous arch drains into the medial and lateral plantar veins. The dorsalis pedis vein, a large deep vein located

on the dorsum of the foot, continues as the anterior tibial vein (Glovzki & MozEs, 2017).

3.Chronic Venous Insufficiency Risk Factors

After a systematic review conducted 20 years after the Framingham Study, Robertson et al. suggested several risk factors including increasing age, positive family history, gender, pregnancy, obesity. Other environmental factors such as decreased mobility at work, smoking, low fiber intake and constipation (Robertson et al., 2008).

4. Prevalence of Chronic Venous Insufficiency

The Vein Consult Program, an international, observational, prospective study involving more than 90,000 patients in different geographic regions, showed that its prevalence is roughly similar worldwide, with a prevalence of 78% in Western countries (Rabe et al., 2012).

5. Chronic Venous Insufficiency Treatment

The most important aim of health services is to make patients feel as good as possible despite the restrictions and necessary treatments brought by their diseases and to help them perform their daily activities (Basaran et al., 2005). In patients presenting with varicose veins or early stage chronic venous disease, conservative treatment with compression stockings is usually the standard treatment option used to reduce symptoms and prevent disease progression (Eberhardt & Raffetto, 2014). Despite the clinical effectiveness of compression stockings, there are many limitations in application, including difficulty in application (fragile or arthritis), physical limitations (obesity, contact dermatitis, sensitive, fragile or weeping skin), and concomitant arterial insufficiency (Raju & Neglen, 2009).

Currently, chronic venous insufficiency is managed by various interventions including conservative care (compression stockings), surgery (high ligation and stripping), ultrasound-guided foam sclerotherapy, endovenous laser ablation, mechanochemical ablation, radiofrequency ablation, and cyanoacrylate embolization (Carroll et al., 2013).

5.1 Chronic Venous Insufficiency and Physiotherapy

Rehabilitation of patients with chronic venous insufficiency includes conservative treatment methods such as wound care, electrotherapy and physical modalities, exercise training, apart from pharmacological and surgical applications (Orr et al., 2017).

Dysfunction and abnormalities of the calf muscle have an important place in its pathophysiology. Gradual exercise programs can be used as an alternative treatment option to rehabilitate muscle pump functions and improve symptoms in chronic venous insufficiency (Eberhardt & Raffetto, 2014).

Manual lymph drainage is a technique that is applied manually and its purpose is to take the lymph fluid from the edematous area and ensure its flow to other parts of the body. With manual lymph drainage, the smooth muscles surrounding the lymph vessels are mechanically stimulated, increasing the lymphatic flow rate and forward movement of the lymph fluid. The proximal part of the extremity is always drained first and then proceeds distally. Going from distal to proximal is contraindicated. The type and sequence of manual technique for each patient is determined by a different principle, which depends on the stage and area of edema (Hafner et al., 1999).

The increase in blood and lymph circulation provides some changes that we can see as secondary mechanisms. With massage, there are changes such as an increase in the movements of the substances that feed the tissues and the formation of a mechanical effect in the blood vessels. These tissue stimulations are the reflex response of the autonomic nervous system and increase blood and lymph circulation (Yates, 2004). It is thought that the effect of massage on the circulation is mostly on the superficial veins, and the results of many studies have shown that the lymph flow increases more during the massage application (Yüksel, 2007; Yates, 2004).

Ultrasound application in chronic venous ulcers provides improvements in pain and edema scores and is effective in reducing wound size and volume and increasing quality of life (Beheshti et al., 2014; White et al., 2015).

In a study examining the effects of low-frequency pulsed magnetic field therapy on edema, quality of life, depression and joint range of motion

in patients with chronic venous insufficiency, it was shown that magnetic field therapy was effective on joint range of motion, edema and depression (Özdemir et al., 2017). Apart from that, vasodilation of blood vessels, increased capillary sprouting, shortened ulcer healing time and increased healing rates have been demonstrated with Galvanic stimulation and high voltage intermittent galvanic stimulation. (Ovens, 2017).

In a study, it was observed that depending on the weakness of the respiratory muscles, blood flow in the legs decreased, vascular resistance increased, and thus it was effective in the formation of venous stasis (Sheel et al., 2001). Significant improvement in quality of life after a 6-week training study consisting of stretching, aerobic, and strengthening exercises in addition to compression therapy, and exercise training in addition to compression therapy were reported to be effective in reducing edema compared to compression therapy alone (Gürdal Karakelle et al., 2021).

In a study in which kinesiotape was applied to women diagnosed with chronic venous insufficiency for four weeks, a decrease in venous symptoms and pain, an increase in venous refill time and venous pump function were found. The only change in the placebo taping group was a decrease in pain, and it was interpreted that this might be due to the placebo effect of taping (Aguilar-Ferrándiz et al., 2014). In another study, “calf” exercises were found to be beneficial in the treatment of chronic venous insufficiency, and additionally, kinesiotape application was found to increase the effectiveness of treatment (Ercan & Çetin, 2017).

In another study examining the effect of different respiratory mechanisms on venous return, it was shown that during diaphragmatic breathing and moderate calf muscle contraction, femoral venous blood flow reached its highest value in both the inspiration and expiration phases compared to mild calf muscle contraction and resting state. This study, which shows the effect of both chest and diaphragmatic breathing on venous return, reveals that the ideal application for increasing venous blood flow is the combination of calf muscle contraction and breathing exercises (Miller et al., 2005).

In studies that compared the effects of dance therapy, which includes steps to strengthen the calf muscle and breathing exercises, with medical treatment on quality of life, functional capacity and disease severity in patients with a diagnosis of venous insufficiency, positive effects on

perceived pain and improvements in quality of life were observed (Huzmeli et al.,2016; Dogru Huzmeli et al., 2020).

In a study aiming to compare combined exercise and calf muscle exercise training on physical activity, fatigue and quality of life in patients with chronic venous insufficiency, 60 people were divided into 2 groups, 30 people in the calf muscle exercise group and 30 people in the combined exercise group. Pumping calf muscle exercise was given to individuals in the calf muscle exercise group, and breathing, pumping exercise, self-massage and hamstring stretching home exercise were given to the combined exercise group. As a result of the 6-week exercise program, a significant difference was found in both groups in terms of physical activity, disease-specific quality of life, cramp pain, and fatigue severity. While a positive effect was obtained even with only calf muscle exercise in the treatment, it was found that the addition of an additional combined exercise program had a greater effect on the disease-specific quality of life and physical activity level, and more positive results were obtained (Çelik, 2022).

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CURRENT DIAGNOSTIC METHODS IN CORONARY ARTERY DISEASES

Ayşegül DURMAZ

- Affiliation: Kocaeli University Faculty of Medicine, Department of Cardiovascular Surgery. Kocaeli/TURKIYE
- ORCID: 0000-0001-5116-4361
- Mail: drayseguldurmaz@gmail.com.tr

Şadan YAVUZ

- Affiliation: Kocaeli University Faculty of Medicine, Department of Cardiovascular Surgery, Kocaeli /TURKIYE
- ORCID: 0000-0001-7566-5531
- Mail: sadanyavuz67@yahoo.com.tr

INTRODUCTION

Coronary artery disease (CAD) is a pathological process characterized by narrowing or occluding epicardial arteries due to atherosclerotic plaque accumulation. (Yalçın H. Canbaz T. H., 2018) The progression of this disease can end with acute myocardial infarction and death. (Townsend N. et al., 2015) The disease's chronic and often progressive nature means it is severe even during clinically silent periods. It can maintain its stable state for a long time. However, it may become unstable at any time due to an acute atherothrombotic event typically caused by rupture or erosion of the atherosclerotic plaque. This process can be changed with lifestyle adjustments, pharmacological treatments, and, if necessary, invasive interventions. (Knuuti J. et al., 2020)

Early diagnosis of risky atherosclerotic lesions is essential in reducing cardiovascular diseases. (Schindler TH et al., 2007) Complete CAD evaluation requires anatomical and functional knowledge. For this purpose, many invasive and non-invasive diagnostic methods are applied separately or in the form of hybrid imaging with the development of technology in recent years. (Tragardh E. et al., 2017)

1. Anamnesis

With a careful history, obtaining a high degree of certainty in diagnosing coronary artery disease is possible. In addition to CAD symptoms, the history should also include information about risk factors such as family history, dyslipidemia, diabetes mellitus, hypertension, and smoking. (Knuuti J. et al., 2020)

Angina pectoris (AP), a typical sign of CAD, is substernal chest pain, pressure, or discomfort. AP is usually felt in the chest, near the sternum, but may spread down the arms, into the neck, into the lower jaw, into the epigastrium, and sometimes into the back. AP may be accompanied by less specific symptoms such as dyspnea, fatigue, weakness, palpitations, or dizziness. The duration of the discomfort is between 5-15 minutes in most cases. Symptoms classically appear or become more severe with increased exertion. Sublingual nitrates and rest relieve angina quickly. (Kloner R.A., Chaitman B., 2017) However, studies show that most suspected CAD patients present atypical chest pain. (Newby DE. et al. 2018)

Table 1. Traditional clinical classification of suspected anginal symptoms from ESC 2019

Typical AP	Meets the following three characteristics: 1. Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm 2. Precipitated by physical exertion 3. Relieved by rest or nitrates within five minutes.
Atypical AP	Meets two of these characteristics.
Non-anginal chest pain	Meets only one or none of these characteristics.

Table 2. Canadian Cardiovascular Society grading of angina pectoris

Grade	Description
Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

2.Physical Examination And Laboratory Tests

There is no specific physical examination finding for CAD, but information about the presence of risk factors can be obtained. Measurement of body mass index and waist circumference within the scope of physical examination is essential for the evaluation to be made in terms of metabolic syndrome. (Girman CJ. et al. 2004) Detection of carotid or peripheral artery disease supports the presence of CAD. Therefore, palpation of peripheral

pulses, auscultation of carotid and femoral arteries, and measurement of the ankle-brachial index can be informative. Physical examination findings of comorbid conditions such as thyroid disease, kidney disease, or diabetes mellitus are significant. (Knuuti J. et al., 2020)

If there is clinical suspicion of CAD instability, such as acute coronary syndrome, it is recommended to measure myocardial injury markers, especially troponin T or troponin I, with repeated measurements if necessary, preferably using high-sensitivity tests.(Reichlin T. et al. 2009; Keller T. et al. 2009)

3. Non-invasive Cardiac Examinations

3.1. Basic Tests in the Diagnosis of Cardiac Ischemia

3.1.1. Chest X-Ray

A chest X-ray imaging does not provide specific information for diagnosis or event risk stratification in CAD. However, it may be helpful to rule out another cause of chest pain in patients with pulmonary problems accompanying CAD or atypical presentations. (Knuuti J. et al., 2020)

3.1.2. Resting and Ambulatory ECG

Electrocardiography (ECG) is obtained by recording the electrical potentials of the heart using electrodes connected to the chest area and extremities of the patient (Devrez N., 2015). A resting ECG should be obtained in all patients with suspected coronary artery disease. (Knuuti J. et al., 2020). Detection of repolarization abnormalities is essential to diagnose myocardial ischemia, especially in a patient with ongoing angina pectoris or similar symptoms. (Knuuti J. et al., 2020). However, a normal ECG does not exclude ischemia. (Durusoy E., 2010) Even without repolarization abnormalities, a 12-lead ECG can detect signs of previous myocardial ischemia (pathological Q waves), left ventricular hypertrophy, preexcitation, and early repolarization pattern, if any. (Durusoy E., 2010) It also provides a basis for comparison in possible future situations (Ertürk E., 2015).

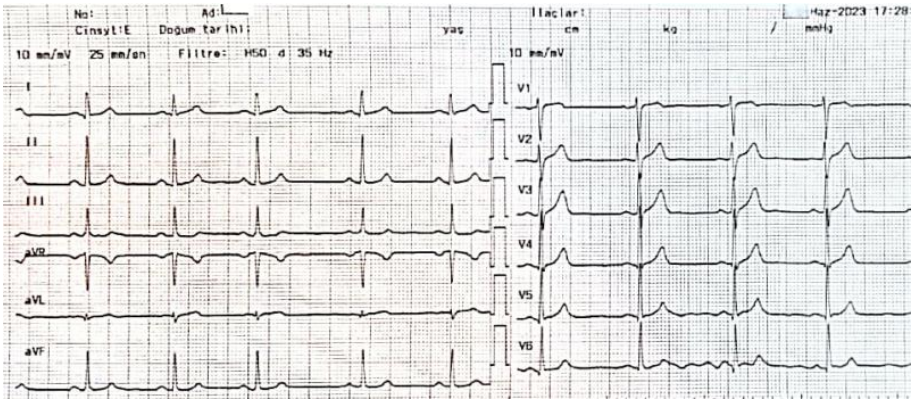

Figure 1. Resting ECG

In selected patients, twenty-four-hour 12-lead ECG monitoring, ambulatory ECG, may be considered to detect angina pectoris episodes unrelated to physical exercise. ECG recording is usually done continuously for 24 hours using a mobile phone-sized device through electrodes attached to the patient's body. Evidence of non-clinical myocardial ischemia can be obtained in patients with ambulatory ECG recording. (Pradhan R. et al., 2012) This examination can also be used to monitor the patient's heart rhythm and blood pressure during his/her daily life. Ambulatory ECG monitoring especially has a role in diagnosing patients with suspected arrhythmia or vasospastic angina. (Montalescot G. et al. 2013)

3.1.3. Resting Echocardiography

Echocardiography is an evaluation method in which the heart's structure and functions are recorded by ultrasound imaging. It is used frequently due to its portability, rapid diagnosis, and non-invasive application. (Ovalı C, Şahin A., 2018) Echocardiography is an essential clinical tool for excluding alternative causes of chest pain. It also helps diagnose heart diseases such as heart valve diseases, heart failure, and cardiomyopathy. (Steeds RP. et al., 2017).

Transthoracic echocardiography (TTE) should be routinely performed in patients with findings consistent with heart valve disease or cardiomyopathy, heart failure symptoms and signs, previous myocardial infarction, and significant ECG changes such as left bundle branch block and pathological Q waves during physical examination. Findings such as decreased left ventricular function and regional wall motion abnormalities detected by TTE may suggest ischemic myocardial damage. (Daly CA. et al.,

2006) It has also been reported that decreased diastolic left ventricular function detected by TTE is an early sign of ischemic myocardial damage and may be significant for microvascular dysfunction. (Nagueh SF. et al., 2016)

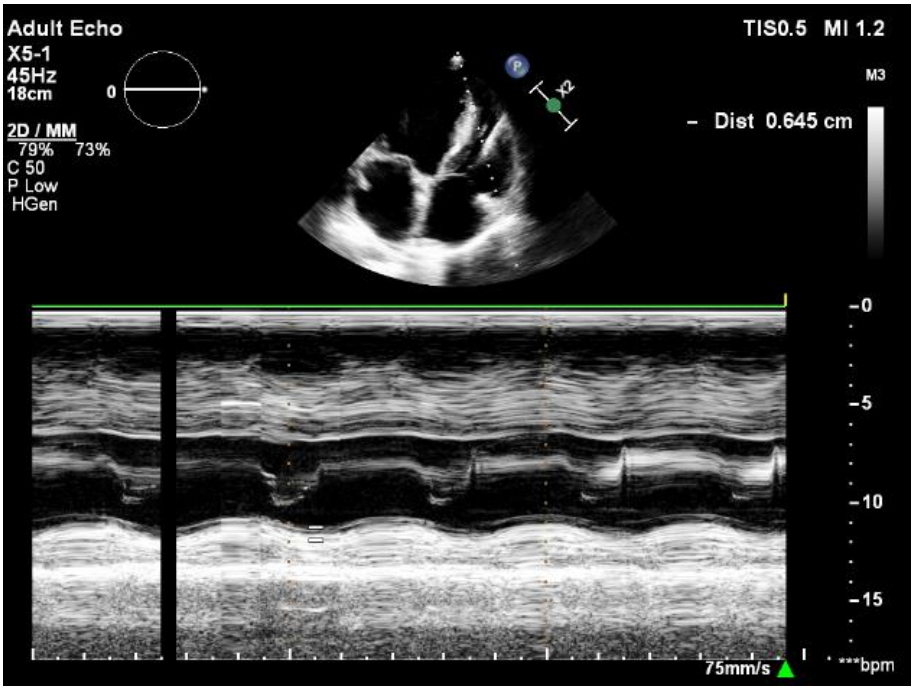

Figure 2. Resting Echocardiography

Transesophageal echocardiography (TEE) is performed with a thin ultrasound probe placed in the esophagus. Since the esophagus passes behind the heart, the heart, its valves, and surrounding vessels can be seen more clearly with this method. TEE is mainly used as a susceptible test to diagnose infective endocarditis, aortic dissection, and left atrial thrombi. (Sicar R. et al., 2008)

3.1.4. Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is imaging the heart in detail via radio waves and taking sections from this imaging. CMR may be considered in patients with suspected CAD when echocardiographic evaluation is inadequate. (Greenwood JP. et al., 2016) CMR is used to identify structural heart anomalies and evaluate ventricular function. Physiological and morphological evaluation of most diseases affecting the large arteries and

veins in the thoracic region and the pericardium and heart is provided (Devrez N., 2015).

3.2. Functional Tests in the Diagnosis of Cardiac Ischemia

3.2.1. Exercise Electrocardiography

Exercise electrocardiography (ECG) is a non-invasive test widely used to diagnose CAD and determine prognosis. Although it is a safe diagnostic tool for appropriate patients, it may not always be sufficient to reveal the presence of CAD in patients with chest pain. (Knuuti J. et al., 2018) It can be considered as a complementary test in addition to clinical evaluation in appropriate patients. (Knuuti J. et al., 2020)

With the exercise ECG, not only the ECG changes but also the heart rate and blood pressure response to the effort, the workload of the heart, the normalization of the findings after the exercise, and the development of angina during the test can also be evaluated. (Durusoy E. et al., 2010)

Indications for termination of exercise testing include pain with significant ST change, significant ST depression (>2 mm relative, >4 mm definite indication), ST elevation, significant arrhythmia, a blood pressure drop of more than 10 mmHg compared to baseline blood pressure, systolic blood pressure exceeding 250 mmHg and diastolic blood pressure exceeding 115 mmHg.(Fletcher GF. et al., 2013) However, the physician's decision can terminate the test in patients with good exercise tolerance and reaching the target heart rate. The false positivity rate is high in patients with left ventricular hypertrophy, digital use, electrolyte imbalance, and intraventricular conduction defects. (Durusoy E. et al., 2010) In cases where electrocardiographic changes cannot be evaluated, such as pace rhythm, WPW syndrome, and complete LBBB, exercise ECG has no value in determining ischemia. (Knuuti J. et al., 2020)

3.2.2. Stress Echocardiography

Regional myocardial systolic function is evaluated by the echocardiographic evaluation during or immediately after stress, apart from rest. Agents such as dipyridamole, dobutamine, and adenosine can be used for pharmacological stress. Although it can be used to locate ischemia, it is not practical. The detection of wall motion defects after exercise is significant regarding coronary artery disease (Steeds RP. et al., 2017). however, its

negative predictive value is higher, and the annual risk of death or myocardial infarction is less than 5% in cases where it is negative. (Jukl L. et.al., 2018)

3.2.3. Myocardial Perfusion Scintigraphy

Nuclear imaging of the heart is performed by detecting with the help of a gamma camera or positron emission tomography and regulating the distribution of radioactive atoms given intravenously that emit gamma rays in the myocardium. In those who cannot exercise adequately, coronary ischemia is usually caused by physical exercise and pharmacological agents such as adenosine, dipyridamole, or dobutamine. The most commonly used isotopes are agents such as thallium 201 and technicium nucleotides. (Ede H. et al., 2015) The main areas of use the myocardial perfusion scintigraphy are the diagnosis of coronary artery disease, risk assessment, acute coronary syndrome differential diagnosis, determination of living tissue, and borderline coronary artery. (Ede H. et al., 2015) Effectively guides the clinician in the presence of appropriate patient selection and clinical situation.

3.3. Non-Invasive Tests Evaluating Coronary Anatomy

3.3.1. Computed Tomography

Computed tomography is an imaging method used to evaluate the structure and function of the heart. Coronary computed tomographic angiography (CTA) accuracy in the detection of obstructive coronary stenosis identified by invasive coronary angiography. This method can perform non-invasive anatomical evaluation by imaging the coronary artery lumen and wall with an intravenous contrast agent. (Knuuti J. et al., 2018) Cardiac CT indications include imaging of coronary arteries, control after revascularization, determination of coronary artery anomalies, calcium scoring, evaluation of coronary plaques, evaluation of right and left ventricular functions, evaluation of myocardial viability and ischemia, valve diseases, coronary venous anatomy, left atrium and pulmonary vein anatomy, congenital heart diseases. (Hazırolan T., 2008) However, stenoses estimated to be 50-90% by CTA examination do not always cause myocardial ischemia; they may not be functionally significant. (Knuuti J. et al., 2018; Tonino PA. et al., 2010)

However, the presence or absence of non-obstructive coronary atherosclerosis in Coronary CTA provides prognostic information and can be used to guide preventive therapy. (Hoffmann U. et al., 2017)

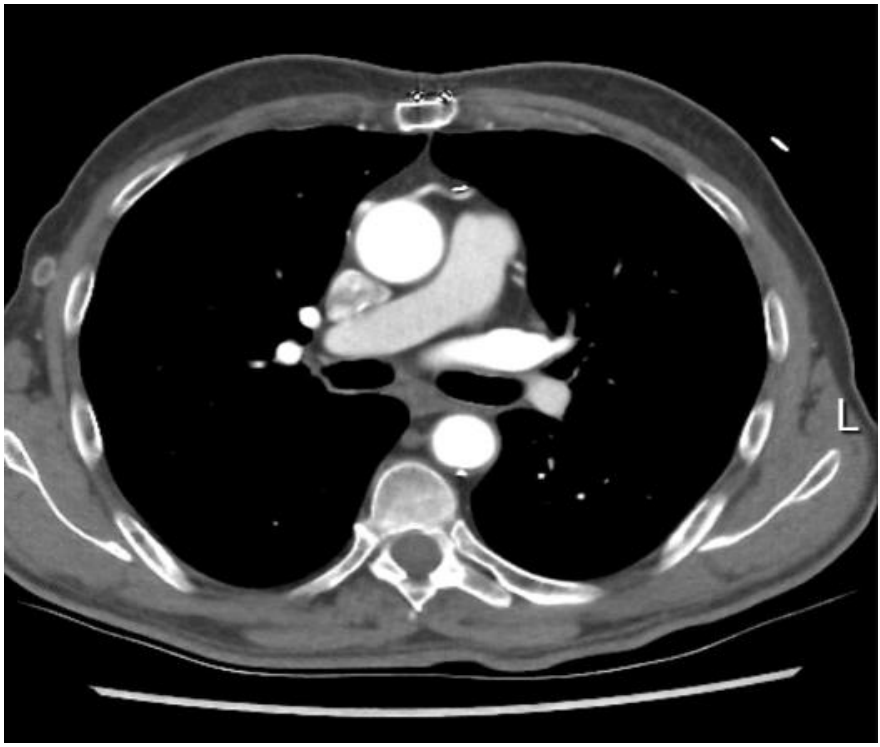

Figure 3. Computed Tomography

Despite the rapid spread of routine use of cardiac CT, more debate still needs to be about its value and indications. The leading reasons for these discussions are the presence of proven alternative methods in the areas where cardiac CT is used and the patient's exposure to X-ray and nephrotoxic contrast material during cardiac CT. (Hazırolan T., 2008)

4.Invasive Cardiac Examinations

4.1. Invasive Coronary Angiography

Coronary angiography (CA) is advancing a catheter inserted through a peripheral artery to the origin of the coronary arteries and imaging the coronary artery lumen anatomy radiographically under x-ray with radiopaque materials given through the catheter. The radial and femoral arteries are the most commonly used peripheral arteries for the entry site. (Reifart Ö. et al., 2022) All coronary arteries and their branches up to 0.3 mm can be visualized using images from certain angles with high-resolution X-ray and serial intracoronary contrast injection (Devrez N., 2015). CA remains the gold standard method for diagnosing vascular stenosis due to coronary artery

disease and determining the appropriate treatment (Tavakol M. et al., 2012). Percutaneous coronary intervention (PCI) can be applied to open the narrowed or occluded vessel detected by CA. Systematic integration of CA with fractional flow reserve has resulted in changes in management strategies in 30-50% of patients undergoing elective ICA. (Baptista SB. et al., 2016)

Significant complications from CA occur in the mouth of 2% of the population, and the mortality rate is less than 0.08%. (Tavakol M. et al., 2012) CA should not be performed in patients with angina who reject invasive procedures and prefer to avoid revascularization, which is not candidates for PCI or coronary artery bypass grafting (CABG), or whose revascularization is not expected to improve functional status and quality of life. (Knuuti J. et al., 2020)

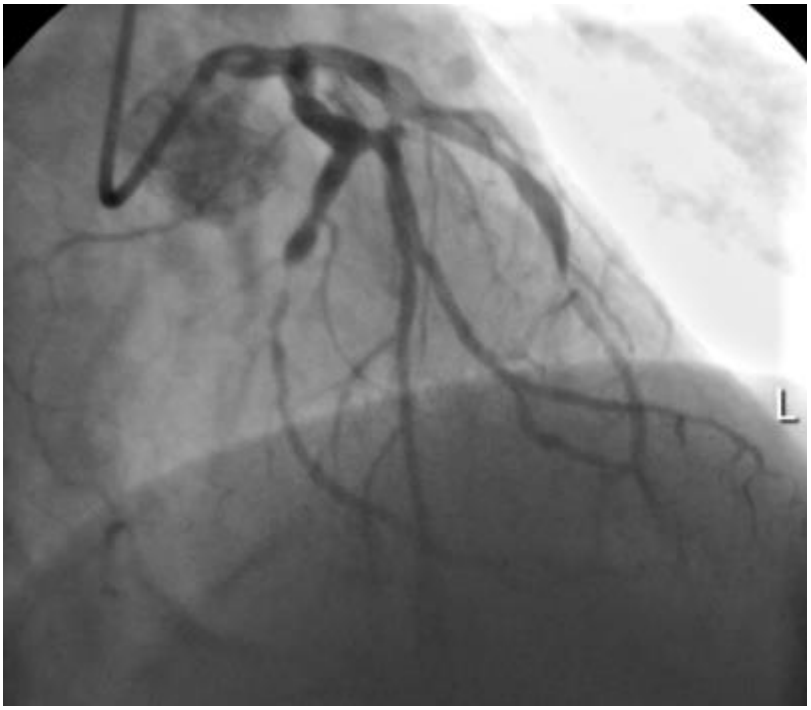

Figure 4. Coronary Angiography

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LUMBAR TRANSFORAMINAL EPIDURAL STEROID INJECTIONS

Ahmet Tolgay AKINCI

- Affiliation: Trakya University, Faculty of Medicine Department of Neurosurgery, Edirne/TURKIYE
- ORCID: 0000-0002-9937-076X
- Mail: ahmettolgayakinci@gmail.com

INTRODUCTION

Low back pain, a primary reason for restricted activity and missed work, imposes high economic and social costs, with billions spent annually on treatment and a high prevalence across various age groups. It affects 4.2% of people aged 24-39 and 19.6% of those aged 20-59; it is a significant global health and economic issue, with annual treatment costs in billions and prevalence rates ranging from 12% to 84% over a lifetime (Rivera 2018).

Low back pain with radicular components, mainly when pain radiates below the knee, is a prevalent condition that significantly impacts pain levels, disability, chronicity, productivity, quality of life, and healthcare resource usage (Spijker-Huiges et al. 2015).

Transforaminal epidural steroid injections (TFESI) are used to treat radicular pain, which is caused by nerve root irritation resulting from impingement or stenosis. These injections are usually administered when traditional treatments like oral medications, physical therapies, and lifestyle changes have not been successful. The procedure involves injecting a corticosteroid into the presumed nerve root. While corticosteroids have a broad spectrum of effects, their primary usefulness in pain management lies in their anti-inflammatory properties, which is why this procedure is frequently performed (Benny and Azari 2011).

In this section, information will be given about lumbar transforaminal epidural steroid injections, which are frequently applied in our Trakya University Faculty of Medicine, Neurosurgery clinic, under the headings of clinical effectiveness and usefulness, effect mechanism, indications, contraindications and techniques. It will be examined with examples from our clinic.

CLINICAL EFFICACY AND USEFULNESS

Today, lumbar transforaminal epidural steroid injections are usually performed under the scope. Its effect is similar to intramuscular injections when an assistive imaging technique such as C-Arm or ultrasonography is not used (Wilson-MacDonald et al. 2005). Nor is it superior to saline injection (Valat et al. 2003). However, it can be beneficial in pain control in the short term, such as 3-6 weeks (Vorobeychik et al., 2016).

When performed with appropriate techniques and imaging, it is very effective, especially in patients with low back pain not alone but with radicular

pain (Landa and Kim 2012; Ökmen and Ökmen 2017; Sharma et al. 2017; Bicket et al. 2015; Manchikanti et al. 2016). Using an assistive imaging technique such as C-Arm or ultrasonography, the duration of analgesia is long, up to 12 months (Landa and Kim 2012; Ökmen and Ökmen 2017; Sharma et al. 2017; Bicket et al. 2015; Manchikanti et al. 2016). It can even save some patients from possible surgery (Bicket et al. 2015).

When the characteristics of the patients are examined, it is seen that some patients benefit more from TFESI applications. These patients' underlying pathology is lumbar disc herniation or lumbar stenosis, a single lesion, and a high Oswestry Disability score at admission (Ghahreman and Bogduk 2011; Fyneface-Ogan 2012). Again, success rates are higher with TFESI in patients who present with central or paracentral disc hernias without excessive root compression and far lateral disc herniation (Fyneface-Ogan 2012; MacMahon, Huang, and Palmer 2016).

When comparing transforaminal and interlaminar techniques in terms of efficacy, there is good evidence that both are effective in pain control and functional recovery at six months (Landa and Kim 2012; Candido 2014). The transforaminal technique seems to be more effective at first (Candido 2014).

EFFECT MECHANISM

Nerve compression is not the only explanatory mechanism of radicular pain. Phospholipase A2, Substance P, VIP, Calsitonine Gene-Related Peptide and many similar inflammatory and neurochemical substances cause sensitisation in free nerve endings, nerve roots and ganglions. Consequently, this leads to radicular symptoms (McLAIN, Kapural, and Mekhail 2004).

Some patients have no clinical signs but have very severe radiological compression, and the opposite can be observed. For this reason, it is thought that the primary effect mechanism of the treatment in TFESI applications is the anti-inflammatory effect of the steroid. However, it is believed that the opening of the epidural space and the change in pressure based on the volume, the neuromodulatory effects of local anaesthetics and the removal of inflammatory agents from the scene also contribute to the analgesic effect. (McLAIN, Kapural, and Mekhail 2004).

INDICATIONS

Transforaminal injections are utilised as a therapeutic strategy for radicular pain, involving the injection of local anaesthetics and corticosteroids

near the nerve roots. This procedure can also be a diagnostic tool to determine the involved nerve when only local anaesthesia is applied. The procedure's objective is to administer the medication directly to the impacted spinal nerve located within the intervertebral foramen, using radiographic imaging for guidance. The procedure is based on the belief that radiographic guidance will ensure precise nerve targeting and that delivering the medication directly to the affected nerve will enhance the likelihood of therapeutic success (MacVicar et al., 2013).

These injections are administered when a specific spinal nerve, or multiple nerves, is suspected of contributing to the pain. Typical reasons for performing Transforaminal Epidural Steroid Injections (TFESI) include herniated discs, radiculopathy, or radiculitis (Rivera 2018).

Around the globe, TFESIs are utilised by healthcare professionals across various departments to treat a broad spectrum of conditions (Friedrich and Harrast, 2010). These include acute, post-operative, and post-traumatic pain associated with hip fractures. They're also used for pain management in post-herpetic neuralgia, pain resulting from vascular occlusion, ureteric colic, and kidney stones. Chronic pain conditions, such as lower back, leg, neck, and arm pain, spinal canal stenosis, pain following herniated disc surgery, pain due to occlusion of leg vessels, and phantom pain experienced by amputees, are also indications for TFSI.

CONTRAINDICATIONS

It would be beneficial to categorise the contraindications for lumbar transforaminal epidural steroid injections into absolute and relative groups. Absolute contraindications are systemic or injection site infection, pregnancy or allergy to any substances to be injected.

Relative contraindications can be listed as convalescent, imminent, mild or other infections, comorbidity, high blood sugar, high blood pressure, coagulation disorder and fear of injection. Here, the use of blood thinners, the iatrogenic state of the coagulation disorder, should be especially mentioned.

Use of blood thinners

There is no definite consensus in the literature on the timing of lumbar TFESIs and the regulation of drugs in patients using blood thinners. There are minor differences in the various guides.

In 2013, the Spine Intervention Society (SIS), previously known as the International Spine Intervention Society, released guidelines outlining the risks linked to different procedures (Bogduk 2013). Subsequently, in 2015, the American Society of Regional Anesthesia and Pain Medicine (ASRA) assessed lumbar TFESIs, among other procedures, and categorised them as having an "intermediate risk" for bleeding complications (Narouze et al. 2015). This assessment was at odds with the SIS guidelines, which indicated that lumbar TFESIs could be safely executed while the patient is on certain blood-thinning medications.

According to the interventional spine and pain procedures guide published in 2018, lumbar transforaminal injections are classified as intermediate-risk interventions (Narouze et al. 2018). The guideline recommends discontinuing antiaggregant and anticoagulants such as aspirin and coumadin five days before the procedure. It recommends that heparin and its derivatives be discontinued 6 to 24 hours before the procedure, depending on their half-lives and the risk of the procedure (Narouze et al. 2018).

Withdrawal of anticoagulants, especially anticoagulants and antiaggregants, prior to spinal injections is standard practice in many clinics. However, recently, different opinions have been expressed on this issue. It has been reported that discontinuing blood thinners to avoid very rare epidural hematomas increases the risk of thrombotic complications, and the latter outweighs the risks of these two complications (Bogduk 2013; Narouze et al. 2015; 2018).

We apply a patient-based approach in Trakya University Faculty of Medicine, Department of Neurosurgery. Generally, in patients with low thromboembolic risk, we stop blood thinners five days before and start again 24 hours after the procedure. In medium and high-risk patients, we apply TFESI without stopping the drugs.

TECHNIQUES

Many injection procedures are applied for diagnostic or therapeutic purposes in the lumbar region. Examples include transforaminal injections with subpedicular or infraneural techniques, interlaminar injections with median or parasagittal techniques, caudal injections and medial branch blocks. In this section, we will talk about subpedicular or infraneural techniques and transforaminal injections.

Subpedicular Transforaminal Technique

The patient is positioned prone, and sedation is typically not required. The patient's skin is cleansed aseptically and covered with sterile drapes (Figure 1&2).

Figure 1. The patient is positioned prone

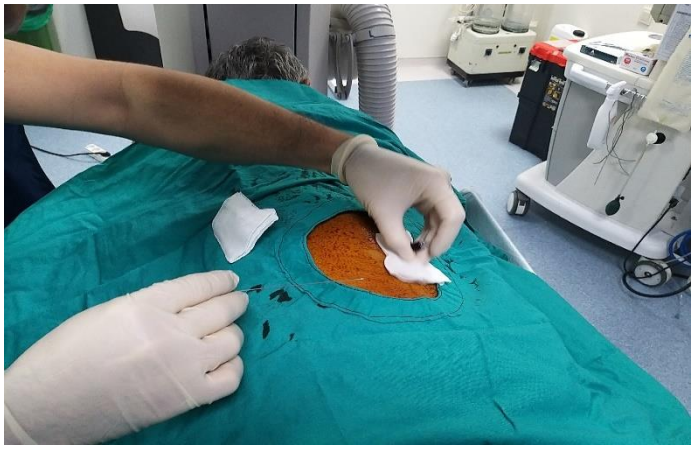


Figure 2. The patient's skin is cleansed aseptically and covered

The targeted segmental level is determined and enhanced in an AP view by aligning the endplates of the target segment. Then, the C-Arm is positioned in an oblique view. The target point is just below the chin of the Scottie Dog. (Figure 3).

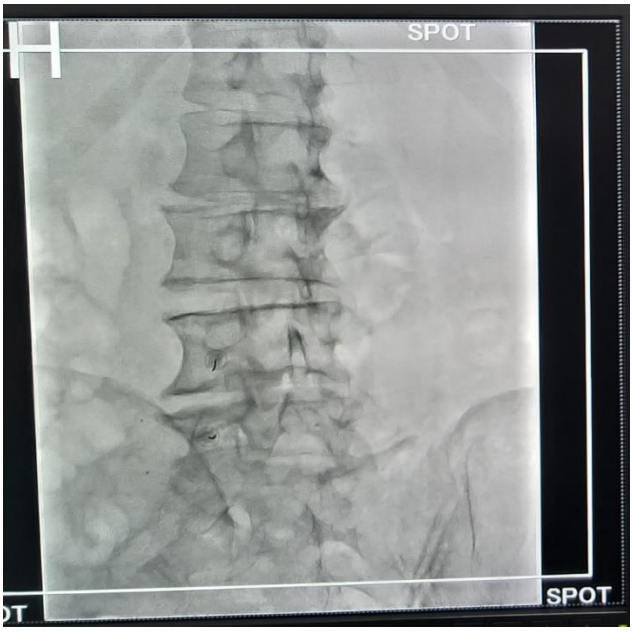


Figure 3. The needle placement

The needle will be advanced until it touches the bone, ensuring the tip remains within the safe triangle area. After making contact with the bone, the C-arm can be adjusted to AP and lateral perspectives to verify the needle's positioning. The contrast dye is slowly administered under live fluoroscopy upon reaching the desired target point. Ideally, the contrast flow should first outline the spinal nerve before it proceeds into the epidural space on the inner side of the pedicle (Figure 4).

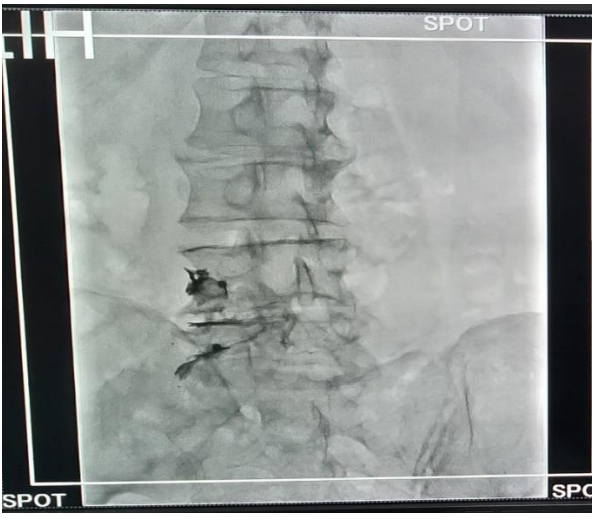


Figure 4. The contrast flow

If there is evidence of arterial or intrathecal flow, the procedure is usually halted to prevent potential complications (Rivera 2018). Subsequently, the medicinal agents are administered.

Infraneural Transforaminal Technique

Infraneural transforaminal epidural steroid injections are also performed without sedation unless necessary for extreme anxiety, and the patient is positioned and prepped similarly. The goal is to position the needle tip just posterior to the disc, within the lower third of the foramen, in a region referred to as Kambin's triangle (Rivera 2018). This right triangle over the disc can safeguard the needle tip from penetrating neural and vascular formations. (Park et al. 2011). In their study, Murthy and his colleagues found that arteries were present in the top half of the foramen 97% of the time and never in the lower fifth (Murthy, Maus, and Behrns 2010).

Utilising an AP projection, the segmental level being targeted is identified and enhanced. Subsequently, an oblique view is acquired. The needle is then introduced and steered towards the lateral lower part of the superior articular process. In the lateral position, the needle is gradually pushed into the posterior part of the foramen. An initial injection of contrast is then performed. There is a possibility of unintentional intradiscal injection (See Case 5). In this case, the needle is pulled back, and the process is repeated.

Another contrast dye injection is performed in the AP view in the final steps. To avoid puncturing the dura, the needle's position should not be medial to the centre of the pedicle. The contrast should flow centrally across the disc space, around the lower pedicle, and along the proximal segmental nerve (Rivera 2018).

Although the subpedincular technique is mainly used in our clinic, both techniques are used, considering the patient's characteristics.

CASE EXAMPLES

Increasing numbers of TFESI have been performed in our clinic, especially in the last decade (Figure 5).

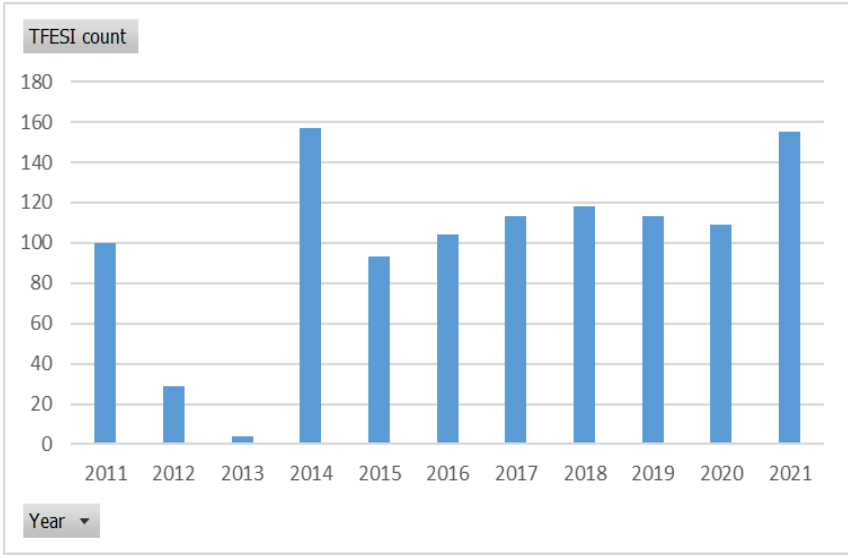


Figure 5. Number of Transforaminal Epidural Steroid Injections (TFESI) by year

Almost all of our clinicians, especially those specialising in the spinal field, apply TFESI (Figure 6).

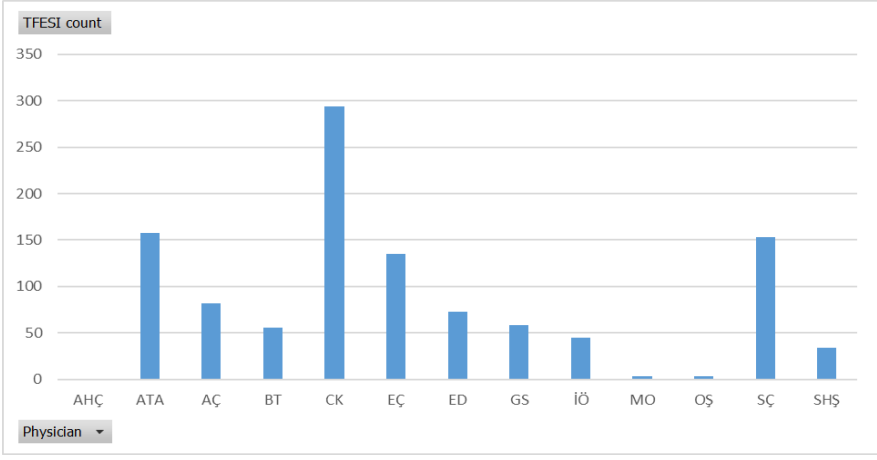
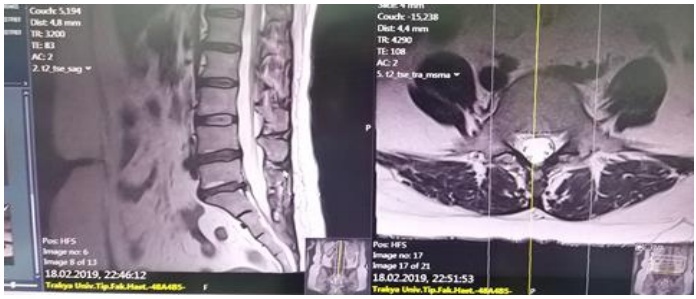
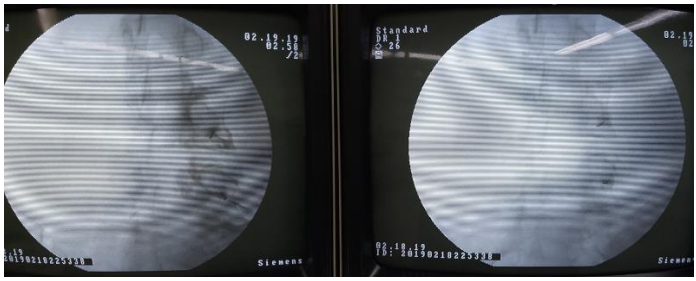


Figure 6. Number of Transforaminal Epidural Steroid Injections (TFESI) by the physician

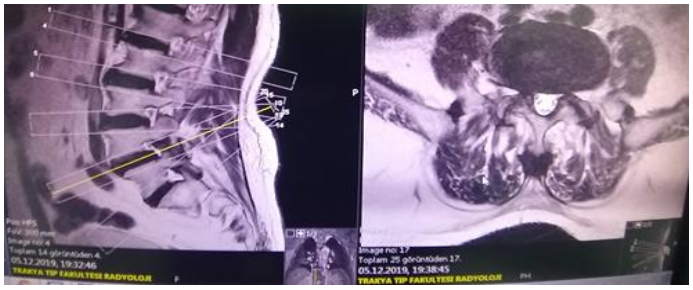
Six examples of lumbar transforaminal epidural steroid injections performed in our clinic for various indications are presented below.

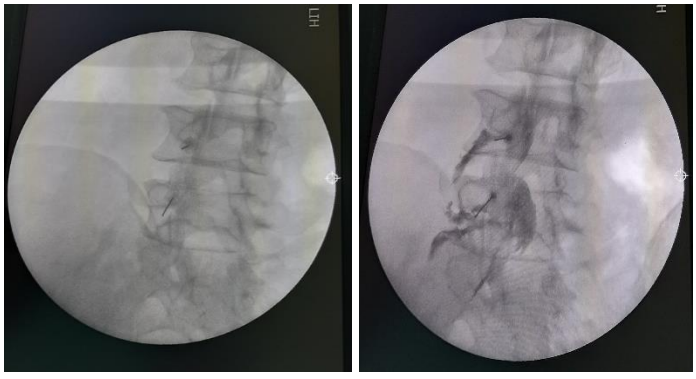
Case 1: A case of discopathy without severe nerve compression.



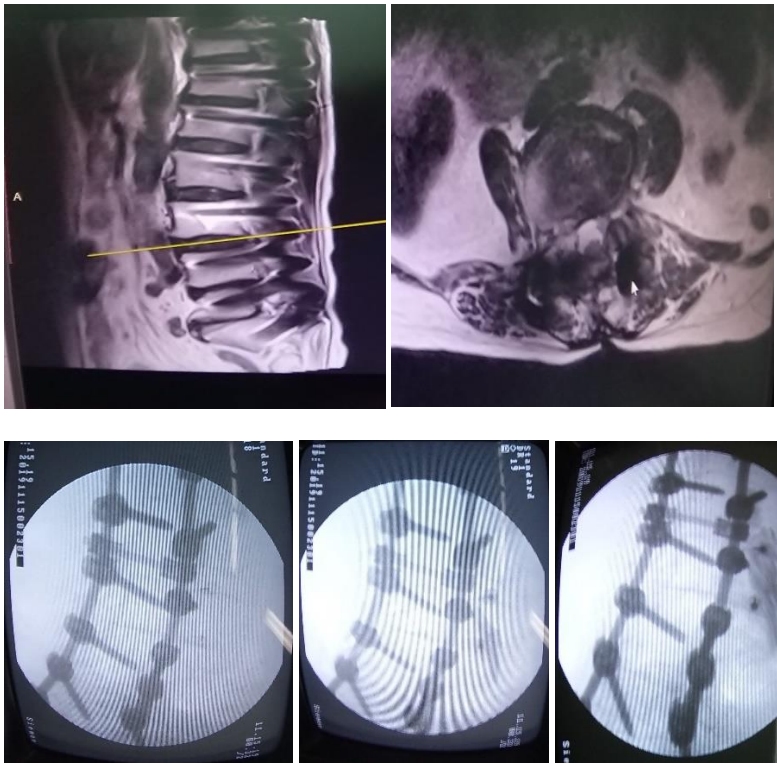


Case 2: A case with new-onset radicular symptoms, foraminal stenosis, but no new/acute disc fragment.

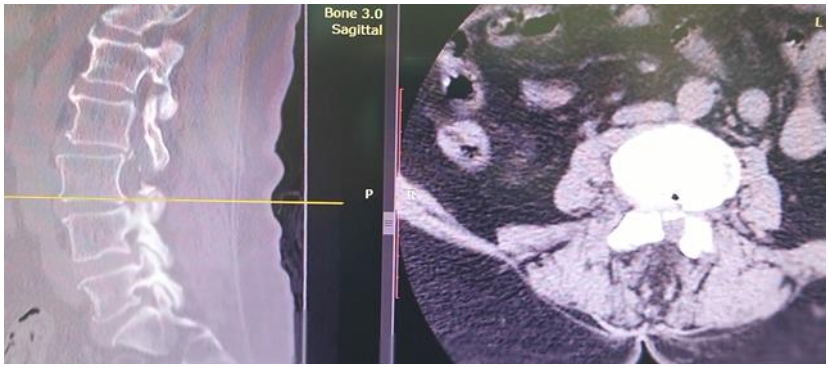


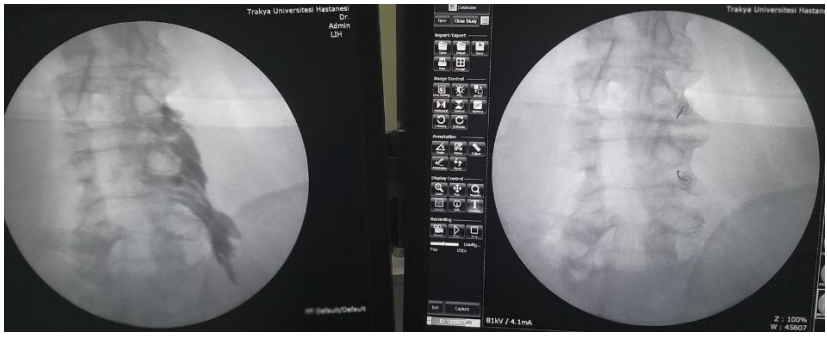


Case 3: A case with a (dysfunctional) instrument, for which we aimed to gain some time before revision surgery.

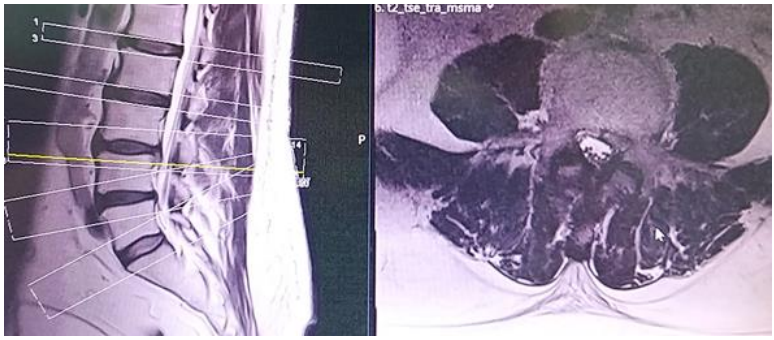


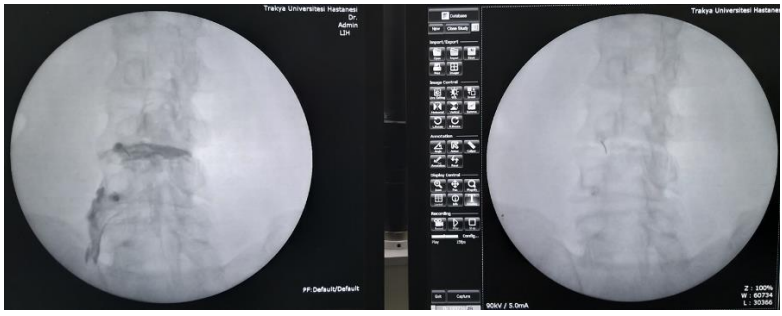
Case 4: A case for which we aimed to support the diagnosis because an MRI could not be performed.



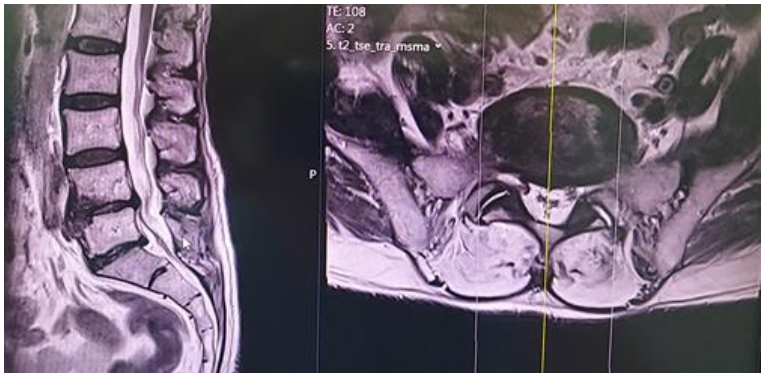


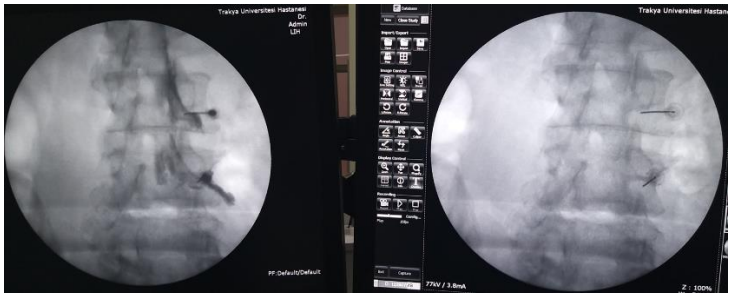
Case 5: In a case with an acute fragment, the injection was performed only through the needle in the L4-5 foramen since we observed intradiscal filling—a colleague of ours who benefited greatly.





Case 6: A case with multilevel pathology, for which we used TFESI as a third referee in distinguishing the affected root as clinical and radiological findings were not matching.





CONCLUSION

Lumbar transforaminal epidural steroid injections do have certain limitations. For instance, they primarily offer anti-inflammatory benefits and do not provide mechanical decompression. Additionally, while the risk is low, potential complications can be a concern. However, the advantages of this procedure are considerable. It is minimally invasive, serves diagnostic and therapeutic purposes—earning it the term 'test therapeutic'—and carries a low risk. Its reproducibility and rapid effects further enhance its value. Given these benefits, these interventions are crucial in bridging the gap between conservative treatment and surgery and should be a part of every practitioner's repertoire.

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CATARACT TYPES AND CURRENT TREATMENT APPROACHES

Göksu ALAÇAMLI

- Affiliation: Trakya University Medicine School, Ophthalmology Department, Edirne/TURKIYE
- ORCID: 0000-0001-5013-9981
- Mail: goksualacamli@yahoo.com

INTRODUCTION

A cataract is a cloudy or opaque area in the normally clear lens of the eye. Cataract types can be classified under 3 main headings according to the morphology, etiology and density of the opacity. The most common classification is the morphological classification (Titiyal et al., 2020; Erol, 2022)

Morphological Classification:

1- Cortical Cataract: It begins as whitish, wedge-shaped opaque areas or lines as a result of regional deterioration of mature lens fibers in the equatorial region of the outer edge of the lens. These opacities are called cortical wedge or cuneiform opacities. It shows slow progress. If the lines extend to the center, it reduces the amount of light passing through, reducing the quality of vision. Glare problems are common with these types of cataracts. This type of cataract, which is usually seen in both eyes, has an asymmetrical course. Without affecting the central region of the lens, the cortical part of the lens condenses to form a cataract (Delcourt et al., 2000; Titiyal et al., 2020).

2- Subcapsular Cataract: It can be examined under two different subheadings, anterior and posterior. In the anterior form, there is opacification in the area adjacent to the anterior capsule of the lens. In the posterior form, there is opacification in the area adjacent to the posterior capsule of the lens. It is the most common type of subcapsular cataract. This type of cataract occurs at an earlier age than cortical and nuclear cataract types. Opacities under the capsule thicken over time and become plaque and may cause complaints of photophobia by increasing irregular light diffraction. This type of cataract can also occur after diabetes, drug use (especially corticosteroids), trauma and inflammation as well as old age (Alapure et al, 2008; Kalantan, 2012).

3- Nuclear Cataract: It is a type of cataract that develops in the fetal nucleus located in the center of the lens. Congenital malformation from microcornea and microphthalmia may accompany this type of cataract. It can cause myopic shift in the eye thanks to its formation in the central region of the lens, which is more dense than its surroundings (Delcourt et al., 2000; Viteri et al., 2004; Erol, 2022).

4-Lamellar Cataract: While the lens is formed during the fetal period, it completes its development in layers. Cataract may develop in the

layer formed at the time of the toxic effect exposed in the intrauterine period. This leads to the typical cataract appearance located in one or several layers of the lens, which appears morphologically in layers. The earlier the toxic exposure, the deeper the cataract formation takes place. It affects vision to varying degrees depending on the density and size of the cataract. Lamellar cataract can be limited to only one layer, or it can turn into a total cataract over time (Francis et al., 2000; Mohanty et al., 2013; Amaya et al., 2003; Erol, 2022).

5-Sutural Cataract: While the lens structure takes its natural shape, the fibrils synthesized by the fetal cells form the lens skeleton in the form of a mesh. This mesh structure is arranged in the form of a straight letter 'Y' on the front of the lens and in the form of an inverted letter 'Y' on the back. The cataract formed at the intersection of these fibrils is called a sutural cataract. It is usually present in both eyes simultaneously. It does not affect vision much, so it is usually detected during a routine eye examination in adulthood (Francis et al., 2000; Mohanty et al., 2013; Amaya et al., 2003; Erol, 2022).

6- Cerulean Cataract: Also known as blue point cataracts, these cataracts are developmental cataracts characterized by blue and white opacities scattered across the nucleus and cortex of the lens. Patients with cerulean cataracts are usually asymptomatic until 18-24 months of age and often do not require surgery until adulthood. The progression of cerulean cataracts is slow, and it may take the third or fourth decade before patients begin to notice a gradual decrease in vision in both eyes. It may be associated with Down syndrome (Ram J, Singh A. (2019).

7- Membranous Cataract: As a rare congenital disease, membranous cataract is characterized by a flattened thick capsule as a result of resorption of lens proteins. The crystalline lens may or may not be fused. Resorption may be traumatic or spontaneous. Cataract appearance occurs when the capsule structure thickens and hardens and turns into an opaque structure. Since there is no regular capsule structure, anterior or pars plana vitrectomy indication may arise, unlike routine cataract surgery (Francis et al., 2000).

Etiological Classification:

1-Congenital Cataract: Congenital cataract is the condition in which the lens, seen from birth, loses its transparency and becomes opaque in one eye or both eyes together. This type of cataract may be caused by the mother's infections during pregnancy, the medications used, or the child's

general health problems (chromosomal abnormalities, systemic diseases such as calcium elevation, etc.). It can occur due to direct or indirect trauma to the eye during birth, or it can occur without any reason (Francis et al., 2000; Amaya et al., 2003).

2) Degenerative (Senile) Cataract: It is the most common type of cataract. Since cataract surgeries are the most frequently performed surgery in the world, it can be said that the most common surgical indication is senile cataract. Physiological changes due to aging cause a gradual decrease in the transparency of the lens, presbyopia, an increase in the scattering and aberration of light waves, as well as deterioration of the optical quality of the eye. This is caused by the decrease in fluid diffusion from the cortex region of the lens to the nucleus region, the accumulation of high molecular weight and insoluble proteins, the formation of crystal aggregates, and the accumulation of glycation end products due to reduced glutathione content. While senile cataract is observed in approximately half of the people between the ages of 50 and 59; It is seen in almost all people aged 80 and over, albeit mildly (Boya et al, 2003).

3) Traumatic Cataract: It occurs due to blunt or penetrating injuries to the eye. It is common in developing countries. Traumatic cataracts have been reported to occur in approximately 27-65% of eye traumas. Nearly half of traumatic cataract cases also have posterior segment damage. Traumatic cataract surgery has some differences and difficulties compared to senile cataract surgery. The aim of surgery is to protect the retina. Among the issues to be considered in this type of cataract are the condition, position, integrity of the lens, the presence of defects in the anterior or posterior capsule, the presence of a foreign body in the vitreous or retina (Khatry et al., 2004; Erol, 2022; Dannenberg et al., 1992; Pieramici et al., 1997; May et al., 2000; Mehul et al., 2011; Kuhn 2010).

4) Secondary Cataract: This is the case of opacification of the posterior capsule of the lens, which may occur a few months or years after cataract extraction. This blocks the passage of light to the retina and leads to vision loss. It can be seen in one of every ten patients undergoing cataract surgery. This is caused by proliferation of epithelial cells, especially in the posterior lens capsule (Kalatan 2012).

5) Toxic Cataract: It is a type of cataract caused by drugs or toxic substances. Although cortisone is the most common toxic cataract agent in daily life, phenothiazine, drugs such as pilocarpine, diuretics, amiodarone,

allopurinol, chloroquine and smoking and alcohol use can also cause this type of cataract. The cataract is typically in the posterior subcapsular region and begins in the optic axis. Therefore, early vision negative effects begin to appear (Gupta et al., 2004; Garder et al., 2012).

Classification by Density:

According to the density of the cataract, it can be staged as new onset, immature, mature, intumescent, hypermature, and morgagnian (Steinert 2010).

Treatment Approaches:

Cataract is an eye disease known since ancient times. The earliest known documentation on the subject of cataracts is the white-painted left pupil of a statue of a clergyman, which is currently in the Cairo Egyptian Museum and dates back to 2457-2467 BC. Neither in ancient Greece nor in the rest of the ancient world there was any information about this disease other than its macroscopic appearance and that it caused a decrease in vision. From prehistoric times to the 19th century, the only treatment method that could partially increase vision was "couching". In this method, the lens is dropped into the vitreous cavity with a curved needle. Although couching has been found to be practiced in some parts of Africa and Yemen until recently, it is a dangerous method that can cause complete blindness and can only occasionally (and very limitedly) increase vision (Yılmaz, 2021; Ascaso & Cristóbal, 2001; Chan, 2010; Savage-Smith, 2000; Rucker, 1965).

French ophthalmologist Jacques Daviel (1696-1762) was the first physician to create a paradigm shift in the treatment of cataracts in the Western world, by both defining and successfully applying cataract extraction surgery. Until Jacques Daviel made ECCE (extracapsular cataract extraction) in 1747, there was no other treatment for cataracts other than couching, which often resulted in blindness (Hubbell, 1904; Barraquer,1966; Williams,2000).

On the other hand, in 1753, Samuel Sharp first documented intracapsular performed cataract extraction (ICCE). In ICCE surgery, the entire lens, including the lens capsule, was removed through a large limbal incision. In the 19th century and the first half of the 20th century, ECCE, not ICCE, was used as a popular surgical method. However, since the 1980s, due to the widespread use of surgical microscopes and the use of modern suture materials and posterior chamber lenses, planned ECCE has come to

the fore. Although EKKE and IKKE were defined in the 18th century, it was not possible to manufacture and implant an artificial intraocular lens that would act as a natural intraocular lens with the technology of the periods before the 20th century. In the 1940s, Nicholas Harold Lloyd Ridley proposed the concept that the use of an intracular lens (IOL) would be more effective and comfortable in the treatment of aphakia after cataract surgery and implanted the first technically successful PMMA intraocular lens in 1949. The acceptance of intraocular lenses in the ophthalmology community has increased with the observation that the risk of corneal damage during IOL implantation has decreased with the introduction of viscoelastic agents since the 1980s. Charles D. Kelman, who was impressed by the ultrasonic devices of dentists in 1967, described the phacoemulsification technique in 1967, in which a metal type moved by ultrasonic vibrations emulsifies the lens material. Phacoemulsification devices have been highly developed since the 1970s. Phacoemulsification surgery is the last major revolution after ECCE and ICCE. Because, in its final form, it has made a dramatic difference compared to ECCE and ICCE in terms of postoperative pain, recovery speed, low astigmatism and better visual acuity, and has replaced them as standard surgery. Today, ECCE and ICCE are only applied in obligatory situations. The phacoemulsification 's real significance compared to ECCE was only with the spread of foldable lenses that allow lens implantation through small incisions (Arshinoff, 2000).

Cataract surgery applied today is still performed using advanced versions of the phacoemulsification device defined by Kelman in 1967. In our country, phacoemulsification on surgery started after 1990 and has been practiced for 30 years. The basic steps of surgery are to apply anesthesia, to make the main incision into which the phaco probe will enter, to fill the anterior chamber with viscoelastic, to perform capsulorhexis and hydrodissection, to cut the lens into several parts and then emulsify it from the eye with a phaco device, aspirate the cortex remnants, and insert the intraocular lens into the capsule. While retrobulbar anesthesia was most commonly used as a method of anesthesia in the past, peribulbar and subtenon anesthesia have come to the fore in time. Today, topical anesthesia is used as a standard. Many methods have been described over the years for fragmentation and emulsification of the lens, but many of them are minor variations of each other (Apple & Sims, 1996; Kelman, 1967; Miller, 1977; Fechner & Fechner, 1983; Liesegang, 1986; Arshinoff, 2000; Arshinoff & Jafari, 2005)

The biggest innovation in recent years is that some stages of phacoemulsification surgery can now be performed with the help of femtosecond laser devices. Today, some femtosecond laser platforms can perform corneal incisions, capsulorhexis and dividing the lens into pieces in the desired number and shape in cataract surgery, and can also mark the axis of the toric lens to be implanted on the capsulorhexis. The most important development in lens technologies is the production of aspheric lenses that compensate or at least not increase corneal asphericity, toric lenses that compensate for corneal astigmatism, and lenses that provide pseudoaccommodation, in addition to monofocal lenses, which were the only option in the past. Since cataract surgeries are now integrated with refractive surgery, correction of presbyopia has also become a goal. The first multifocal lenses used for this purpose were of a diffractive or refractive design and had two focal points for near and far (bifocal lenses). Most multifocal lenses today have a rotationally symmetrical diffractive design and 3 focal points (trifocal lenses). However, rotationally non-symmetrical bifocal design, extended depth of focus (EDOF) and adjusting the asphericity of the lens are other approaches used in lens designs of various companies in order to provide spectacle independence at medium and close ranges (Kane et al., 2016; Wan et al, 2019; Abulafia et al., 2016).

It is now largely possible to remove the cataract lens with almost no damage to the eye, but of course, new surgical or non-surgical methods will be developed in the future to make this procedure much simpler and with a lower risk of complications.

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THE IMPORTANCE OF THE ANATOMICAL STRUCTURE OF MAXILLARY SINUS IN ORAL AND MAXILLOFACIAL SURGERY: A REVIEW OF THE LITERATURE

Raha AKBARİHAMED

- Affiliation: Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ankara Medipol University, Ankara/TURKIYE
- ORCID: 0000-0003-3401-2117
- Mail: raha.akbarihamed@ankaramedipol.edu.tr

Hacer EBERLİKÖSE

- Affiliation: Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ankara Medipol University, Ankara/TURKIYE
- ORCID: 0000-0003-1450-1968
- Mail: hacer.eberlikose@ankaramedipol.edu.tr

Arif Yiğit GÜLER

- Affiliation: Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ankara Medipol University, Ankara/TURKIYE
- ORCID: 0000-0002-9962-4926
- Mail: arif.guler@ankaramedipol.edu.tr

INTRODUCTION

Due to its anatomical localization, the maxillary sinus has an important role in maxillofacial surgery. A piece of good knowledge about the maxillary sinus region is very important for the operator to minimize the risk of complications during surgical operations like Le-Fort I osteotomy, Caldwell-Luc operation, maxillary sinus-related tooth extraction, and dental implant surgery. Inflammatory diseases or structural changes in the maxillary sinus region have a serious impact on the surgical success. The so-called osteomeatal complex (OMC) is the most critical region in the formation of sinus diseases. Osteomeatal complex is the name given to the whole anatomical structures in the middle meatus on the ethmoid bone. Uncinate process, hiatus semilunaris, bulla ethmoidalis, ethmoid infindubulum, primary ostium maxillaris, middle turbinate and frontal recesses constitute the osteomeatal complex. A contraction in any of the passages, primary ostium maxillaris, ethmoid infundibulum, and hiatus semilunaris in the OMC may cause a maxillary sinus pathology. Mantoani et al. stated that a maxillary sinus is healthy when the mucous outflow is normal, mucociliary clearance is efficient and the ostium is patent.

For the better assessment of this critical area, cone-beam computerized tomography (CBCT) images should be evaluated carefully in the daily routine. It is thought that a detailed examination of the related area with CBCT before surgery will make it possible to avoid intraoperative and postoperative complications.

For this reason, the anatomical structures in the maxillary sinus and osteomeatal complex are investigated and a literature review about the effect of the changes on the maxillary sinus was made.

Anatomical and Physiological variations

Presence of teeth

Primarily, Shangbang et al. detected that Schneiderian membrane (SM) thickness is higher than 2 mm and reduced residual ridge heights (4 mm) were highly prevalent in patients with teeth loss. Aksoy et al. declared that posterior edentulous maxillae were associated with significantly higher thickening of the SM (>2 mm). Sigaroudi et al. observed no significant relationship between teeth loss and septa prevelance(8). Khojastehpour et al. stated that the distances between Posterior Superior Alveolar Artery (PSSA)

and the medial sinus wall along with the diameter of the artery are statistically linked with the number of teeth loss. In the same study, the authors confirmed that PSSA observed by CBCT is associated with a higher mean number of missing teeth. Jang et al. detected that there is no significant difference in septum prevalence between dentulous and edentulous patient. In light of all these factors, the maxillary sinus collapses vertically and this may cause difficulties during sinus surgery.

Sinus Pneumatization

Maxillary sinus pneumatization is the most observed anatomic variation. Lana et al. have decided to focus on this parameter and detected sinus pneumatization in 83.2% of the patients. Schriber et al. noted that following tooth loss in the posterior maxilla, the vertical bone height is primarily lost due to resorption of the alveolar crest, and not due to pneumatization of the maxillary sinus. Shahidi et at observed this in 24.2% of the patients' anterior sinus pneumatization. A palatonasal recess is the extension of the maxillary sinus into the nasal floor. This ectopic pneumatization of the maxillary sinus may cause difficulties during the open sinus surgery. A serious pneumatization of the maxillary sinus can lead to problems during dental implant surgery.

Posterior superior alveolar artery

The maxillary artery provides the blood supply to the maxillary sinus with 4 main branches: the posterior superior alveolar artery (PSAA), the infraorbital artery, the descendent palatine artery, and the sphenopalatine artery. The branches of the superior posterior and anterior alveolar artery supply the maxillary sinus floor and Schneiderian membrane. These arteries run through the superior alveolar canal, which is divided into two segments: The posterior superior alveolar canal (PSAC) and the anterior superior alveolar canal (ASAC). It is stated that in 10% to 30% of the cases, the PSAA artery is located in the surgery area for the lateral window sinus floor technique. Mardinger et al. observed that the PSAA had an ascending and descending track in anterioposterior direction and the lowest point is 20 mm from the posterior sinus wall. Most of the measurements in the studies are performed at this point. Nicolielo et al. stated that the PSAC was observed in 73.5% of the patients. PSAC was observed in 48.60% of the Caucassian patients. Velasco-Torres detected bilateral PSAA in 77.15% of the patients. PSAA's distance to the medial sinus wall and the alveolar crest is found to be longer in males as to females.

Localization

The localization of the PSAA was detected as 13.15±3.71 mm from the alveolar crest. Velasco-Torres made a measurement from the sinus floor (mean= 6.86mm). They also made a measurement from the alveolar crest (13.40 ± 3.72 mm). The authors disclosed that the distance of the artery from the sinus floor also correlates with gender. In females, the distances are significantly shorter than in males. In the same study, the authors observed a relation between age and sinus floor distance. The PSAA distance from the sinus floor gets lower with an increase in age. Only 75% of the PSAC were subperiosteal to the Schneiderian membrane. %43 percent of the anastomosis of PSAC and ASAC were between the canine and first premolar. These differences may be explained by the anatomic variations in the position where the artery was first seen. The most common position at which the artery was first visualized was the first molar area (46.15%). With the vertical collapse of the maxillary sinus, the position of the PSAA can change with age and tooth loss. Nicolielo et al. stated that a measurement made from the alveolar crest would be a better reference for an oral surgeon during implant surgery.

Alveolar-antral-artery

The anastomosis between the PSAA and the infraorbital artery is called the alveolar antral artery (AAA)(5). Sun et al. detected in 87.6% of the patients, the alveolar antral canal is in a mean distance of 9.2± 3.5 mm to the maxillary sinus floor. Valente et al. stated that on CBCT the detection rate of the anterior alveolar artery is determined by the experience of the radiologists or clinicians. The diameter of the anterior alveolar artery vessels is smaller than 1 mm. The mean distances of the AAA from the alveolar crest and sinus floor range from 11.25 mm to 26.90 mm and 5.80 mm to 10.40 mm. A double window osteotomy or a caudally shifted osteotomy window can be preferred to avoid bleeding during surgery.

Mucus Retention Cyst/ANTRAL PSEUDOCYST

The reason for antral pseudocysts is the accumulation of inflammatory exudates in the sinus membrane. The inflammatory character of the pseudocyst increases the tension of the sinus membrane, and this can increase the risk of perforation during the sinus lift procedure. Yeung et al. revealed that 12.9% of the patients showed mucus retention cysts. Akay et al. observed maxillary sinus radiodensities in 45.1% of the patients. For the

left maxillary sinus, a statistically significant relationship between gender and sinus pathology was present. Tassöker et al. detected that concha bullosa, nasal septum deviation, and septa are not predisposing factors for sinus pathologies. Yalcın et al. detected a significant relationship between maxillary sinus pathologies and the prevalence of PSSA. It is very controversial to perform sinus lift operation in patients with pseudocyst. For some authors, the presence of pseudocysts is a contraindication for sinus lift procedures. Some other authors stated that perforation risk does not increase with the presence of pseudocysts. The size of the pseudocyst is important because a corruption of the maxillary outflow may occur with the manipulation of the Schneiderian membrane. Although Quin et al. stated that the implant survival rates and sinus floor elevation carried out by the osteotome technique are not affected by antral pseudocyst or flat membrane thickening. Pathological changes that occur preoperatively in the maxillary sinus may lead to failure in 18-20 months after the surgical operation. But studies have reported that pathological lesions do not constitute a definitive contraindication for sinus floor elevation surgeries.

Membrane thickness and perforation

Local anatomical and patient-related factors may affect the physiology of the Schneiderian membrane and the sinus lift procedure. Lozano-Carrascal stated that in 72.9% of the patients, the Schneiderian membrane thickening was lower than 3 mm and in 27.10% of the cases, the membrane thickness was higher than 3 mm. Aksoy et al. detected that in the Turkish population, 45% of the patients have a Schneiderian membrane thickness of more than 2 mm. Despite that Akay et al. declared a membrane thickening more than 2 mm was observed in 25% of the patients. In most of the studies performed, a higher mucosal membrane thickening was present in males. In the same study; 63.2% of the patients had moderate and severe periodontal bone loss and this was statistically connected with more than 2 mm Schneiderian membrane thickening. Tavelli et al. published in their systematic review that some authors revealed that a membrane thickness of more than 5 mm increased the risk of ostium obstruction. The perforation risk is higher if the Schneiderian membrane thickness is less then 1-1.5 mm. Tavelli et al. classified the Schneiderian membrane thickness according to the difficulty of manipulation. Rapani et al. detected that membrane perforation up to 8% (12 patients) occur with a Schneiderian membrane thickness of 0 mm. They also observed the Schneiderian Membrane perforation in 4 patients with a membrane thickness of 2-3.5 mm. In another

study, Wen et al. stated that the lowest perforation risk was with a Schneiderian membrane thickness of 1.5-2 mm. Wen et al. also observed that the perforation risk increased when the Schneiderian membrane thickness is lower than 0.5 mm or higher than 3 mm. Ramanauskaite et al. revealed that a flat membrane thickening without a well-defined border is the most frequent morphological abnormality of the Schneiderian membrane. Zimmo et al. stated that a relation between age and membrane thickness was observed. Some authors showed that the Schneiderian membrane had osteogenic potential for bone formation. A membrane higher than 5 mm must be consulted to the ENT doctor and if necessary a medical treatment of the sinus conditions should be considered.

Sinus Septa

Sinus septa are well documented maxillary sinus entities. Maxillary sinus septa vary in height, size, prevalence rate, position, and orientation. Lozano-Carrascal et al. used the classification according to the orientation of the septa. The most detected septum is the bucco-palatinal sinus septum, which height is revealed as 13.11±3.82 mm from the alveolar crest. The sagittal orientated septa are present in 3.74% of the cases with a height of 12.24±1.25 mm. Taleghani et al. stated that in 44 % of the patients, a sinus septa is observed. Tavelli et al. revealed that most of the authors declare that the presence of a sinus septa increases the risk of perforation. In a study performed in 2015, the authors confirmed that the presence of a septum increases the Schneiderian membrane thickness. Dragan et al. detected complete sinus septa in 98% in dentate and in 96% in edentate patients. Therewithal, the authors declared that the septum is mostly present in the posterior maxilla around the second molar region. If the sinus septum runs longitudinal or is incomplete, the surgery gets more difficult; but transversal complete sinus septa does not affect the difficulty of the operation. Taleghani et al. claimed that a statistically significant difference in the height of septa is present between females and males ($p<0.01$ females: 3.33 ± 1.42 mm; males: 4.08 ± 1.64). Demirkol et al. examined the relationship between maxillary sinus septa and alveolar bone height and found no statistically significant relationship.

Angle of the buccolingual maxillary sinus wall

The definition of the buccolingual maxillary sinus wall angle is made as to the angle between the vestibular and palatinal sinus walls. Cho et al. stated that a buccolingual wall angle lower than 30º decreases the risk of

perforation. However, another theory is that if the sinus walls are closer, the greater the blood supply to the grafted area will be. Rahpeyma et al. stated in their systemic review that very sharp angulation is a reason for difficult sinus lift surgeries.

Buccal bone thickness

A difference in buccal bone thickness was observed between partial edentulism and complete edentulism. Kiakojor et al. measured buccal bone thickness of 1.31 ± 0.3 mm in partial edentulism and 0.95± 0.26 mm in patients with complete edentulism. In females, a buccal bone thickness of 2.11 mm was observed in the first premolar region. In the same study, the thickest area was measured 9.87 mm in females and 10.71 mm in males. A significant relation between residual height and buccal bone thickness was observed. To best of our knowledge, chronic inflammatory diseases like chronic periodontitis may influence the buccal bone and also sinus lateral bone wall thickness. With a thick buccal bone, the open sinus lift procedure becomes more difficult.

Residual alveolar height

Generally, the residual alveolar height is measured at the points of the maxillary second premolar, first molar or second molar. Lozano-Carrascal et al. performed a measurement of the residual alveolar height in Caucasians; in the location of the maxillary second premolar, the residual alveolar height was 8.66±3.95 mm; 4.90±2.28 mm at the first molar; and 5.26±2.13 mm at the second molar. Cavalcanti et al. stated that a minimum residual alveolar height lower than 5mm has appeared at the second premolar region. In the same study, the highest residual alveolar height was around the first molar (>8mm). Khojastehpour et al. stated that the PSAA diameter and frequency are higher in a patient with a residual height of <10mm.These findings suggest that sinus pneumatization prior to extraction doesn’t predispose to a more pronounced migration of sinus floor towards the ridge, but may result in a decreased residual alveolar height. A statistical relation was observed between residual ridge height and perforation risk. With the transcrestal sinus approach, the perforation risk increased when the residual crest height is higher than 11mm or lower than 2mm. Wen et al. stated that the lesser the residual alveolar height is, the thicker the Schneiderian membrane is.

Endodontic treatment

The authors stated that teeth with periapical lesion and a close relationship to the maxillary sinus increase the prevalence of mucosal thickening (> 2 mm) to 64%. Investigation showed that sinus membranes in contiguity with apical lesions tend to be thicker. Tassöker stated that one apical lesion concerning the maxillary sinus increased the maxillary sinus pathology by 4 to 5 times.

Primary Ostium Maxillaris

Primary ostium maxillaris (POM) is an important anatomical structure. The generally oval-shaped POM allows the maxillary sinus to open into the nasal cavity. While a healthy POM provides drainage of the maxillary sinus to the middle meatus located in the nasal cavity, it affects the health of both the Schneiderian membrane and the maxillary sinus. Shangbang et al. stated that a polypoid membrane thickness causes primary ostium maxillaris obstruction. The authors revealed a significant relationship between ostium height and the presence of maxillary sinus septa. POM contraction or complete obstruction causes maxillary sinusitis. It can also affect paranasal sinuses and cause pansinusitis. In other words, sinus pathologies can occur not only with dental pathologies but also with ostium narrowing.

Accessory maxillary ostium

Accessory Maxillary Ostium (AMO) is the second opening in the medial maxillary wall that connects the maxillary sinus to the nasal cavity. AMO can occur between the uncinate protrusion and the inferior concha. It occurs at low resistance points on the lateral nasal wall. The reason for the formation of low resistance points is that it is composed of only a combination of nasal and sinus mucosa with no bone support. This area is also known as "fontanelle". In the literature, it has been reported that fontanelle occurs due to infection and edema occurring in recurrent sinusitis. So the role of accessory maxillary ostium (AMO) is very controversial. Some authors stated that the AMO is an anatomical variation and others declared it has a pathological character that may lead to chronic sinusitis. Investigation showed accessory ostium maxillaris in 47.2% of the patients. The authors detected the AMOs in the nasal fontanelle region (81.1%). The shape of the ostium is for most cases, in ovaloid (48.4%) or round shape

(39.0%). Investigation showed AMO in 40.8% of the patients in the Turkish population.

Fractures and previous surgeries

Rahpeyma et al. stated that previous Cadwell-Luc surgeries can cause oroantral fistula. A technique used for the replacement of medial maxilla fractures is the method applied by placing a thin elevator in the accessory Maxillary Ostium. While the orbital floor is corrected by transmaxillary reduction, a balloon is placed in the nasal cavity through the maxillary ostium.

Nasal septum deviation

Nasal septal deviation increases the risk of blockage of the middle meatus and also, the obstruction of the maxillary ostium. This is a predisposing factor for complications during sinus lift procedure. Akay et al. detected the nasal septum deviation for Turkish population as 74%.

Concha Bullosa

Concha Bullosae are one of the anatomical variations that can occur in the osteomeatal complex. The presence of concha bullosa is an etiological factor for maxillary sinusitis. In Turkish population, the concha bullosa prevalence was 36.8%.

CONCLUSION

This study starts with the aim of assessing the effect of different orofacial conditions in maxillary sinus operations. Different anatomic landmarks like the sinus floor or the alveolar crest could be used as orientation points to avoid possible complications. In this clinical standpoint, it is essential to perform a profound presurgical study, so that the surgical technique can be modified during surgery and complications may be reduced.

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CLOSED RHINOPLASTY

Ahmet KÖDER

- Affiliation: Trakya University Medical Faculty Otorhinolaryngology Department, Edirne/TURKIYE
- ORCID: 0000-0003-4348-8109
- Mail: ahmetkoder@yahoo.com

INTRODUCTION

Rhinoplasty is an operation applied to change the external appearance of the nose. Its frequency is increasing nowadays. The widespread use of the internet and social media increase the demand for operations. This operation can also be performed in the form of a septorhinoplasty operation in people with nasal congestion. Rhinoplasty operation can be performed with open or closed technique (Alexander, 1995; Berghaus, 2016; Tasman,2007) These techniques are not superior to each other. Both techniques have their pros and cons relative to each other. Today, most surgeons prefer open surgery in revision cases and traumatic noses. Some surgeons, on the other hand, perform all their surgeries, including revision, with a closed approach. There are two basic parameters in the choice of open or closed approach, the first is the preference of the patient and the second is the preference of the surgeon.

Examination

It is very important to evaluate the patients who apply with the request of rhinoplasty. Surgery should not be decided immediately after the first interview. It would be appropriate to have at least two interviews to get to know and analyze the patient better. It is necessary to allocate enough time for the patient to understand exactly what he wants and to explain his problems as he wants. It is very important to analyze the patient well in order not to encounter post-operative problems. If the patient's wishes and our surgical plan are in harmony with each other, the operation should be planned. Some patients may have unrealistic expectations or our surgical style may differ from the type of nose the patient wants. The greater the difference between the nose that the patient plans and imagines in his head and the nose we did during the surgery, the bigger the post-operative problem. We may think that we performed a good operation, but if the operation we perform does not meet the expectations of the patient, the patient will be unhappy. The best way to prevent all these is to analyze the patients well before the surgery and not to have surgery on everyone who applies to us. It is necessary to know how to refuse the patient when necessary. In the examination, bone roof, middle roof and tip area should be evaluated separately. The patient's skin thickness and skin structure should be analyzed. The inside of the nose must be evaluated from the nostril to the nasopharynx with the help of an endoscope. In the nose, the septum, inferior turbinates, middle turbinates and nasopharynx should be evaluated

separately. Ready-made templates can be used to fully evaluate the internal and external structures of the nose. Findings in the examination can be noted on these templates. Things that are planned surgically can be noted.

Photographing

Photography is an essential part of rhinoplasty surgery. It is necessary to photograph the patient's nose in a standard way and at angles, both in terms of medicolegal aspects and to see the result of our own surgery and for follow-up. The patient can be directed to the photographer and photographed with the paper that details the angle and plan we want for photographing, but today, almost all surgeons dealing with rhinoplasty take their own photographs. When taking a photo, attention should be paid to the standard angle, light and background. All photographs must be taken with the same camera and lens in order to make an objective comparison. For a good photograph, the light should come from behind and paraflash should be used. A 50 or 100 macro lens can be used. The photo is taken in portrait mode. Also, a dark background should be preferred.

Surgical Set

Each surgeon may have different instruments in their rhinoplasty set. It is possible to perform closed rhinoplasty surgery with approximately 25-30 pieces of instruments. Figure (1).

Retractor: A dorsum retractor with fine edges and a blunt tip is required to retract the dorsum. A small retractor is required for elevation, especially after the first incisions.

Scissors: Straight and curved scissors with long and short handles are required for elevation and excision. Super cut scissors can be used, but care must be taken not to make an uncontrolled cut. Bone or turbinate scissors can be used to cut the bone septum.

Forceps: Multitooth or toothless forceps can be used to hold cartilage grafts and tissues, and single-toothed forceps can be used to hold mucosa.

Needleholder: A thin needleholder is required for suturing.

Rasp: Back rasp to correct bone hump at my dorsum, A fine rasp to shape or refine bone sidewalls, and radix rasp to reduce radix in high radix patients.

Saw: Some surgeons perform the osteotomy with a saw. A lateral saw is required for lateral osteotomy, and a 90 degree angle saw is required for transverse osteotomy. Paramedian osteotomy can also be done with a lateral saw.

Osteotome: Most surgeons perform osteotomies with osteotomes. Lateral osteotomes for lateral, 2 or 3 mm flat osteotomes for paramedian or median osteotomy. Median osteotomes can be used to resect cartilage and bone hump. 1 or 2 mm osteotomes can be used to reduce radix. 2mm osteotomes can also be used for percutaneous osteotomy.

Elevator: A cottle elevator can be used for septum dissection, and a periosteal elevator can be used to elevate the periosteum of the nasal bone at the dorsum.

Hook: Double or single hooks can be used for hooking.

Arkansas stone: Used for sharpening tools.

Nasal speculum: Used to dissect the septum, for injection into the septum, and to see inside the nose. One small, medium or large speculum is sufficient.

Hammer: Required for hitting osteotomes and hitting the base guj.

Guj: It is used to remove the basal crest inside the nose.

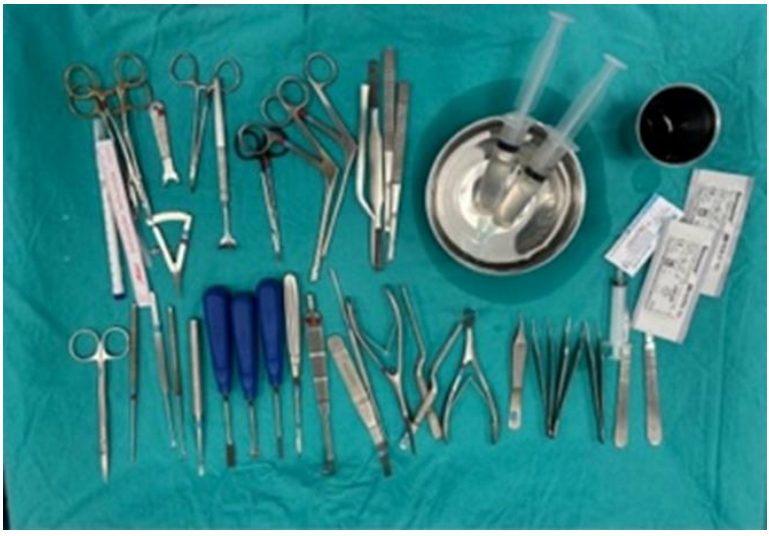

Figure 1: Surgical Set

Operation Steps

Patient Position

The patient should be lifted approximately 30 degrees from the waist. The head should be parallel to the ground. The intubation tube is fixed in the midline. Some surgeons want to see the chin completely by putting the intubation tube aside. If the intubation tube is desired on the side, care should be taken not to pull the cheek and lip laterally. Sponge can be placed in the mouth to prevent blood leakage from the posterior during the operation**.**

Local anesthesia

After the patient is intubated, pads with xylometazoline, oxymetazoline or pseudoephedrine are placed in the nasal passage. These pads shrink the lower turbinate, making the nasal passage better visible, and also help control bleeding. If pads are not wanted to be placed in the nasal passage, xylometazoline or oxymetazoline spray can be sprayed directly. Two cuffs are sufficient for each nostril. After this procedure, local anesthetic is administered. As a local anesthetic, different surgeons may use different preparation solutions with different concentrations. As a local anesthetic, 1/100000 adrenaline solution can be used. Care should be taken when injecting, and it should be ensured that the injection is not made directly into the vein. Injection should be done slowly and while injecting, the patient's blood pressure change and tachycardia should be observed. In case of tachycardia or increased blood pressure, the injection should be interrupted. It should take approximately 15 minutes for the full effect of the local anesthetic to be seen. For this reason, the injection should be done immediately after the patient is intubated, and then the steps of sterilization and covering the patient should be started. Local anesthetic is applied to the anterior nasal spine, nasal dorsum, septum lateral crus caudal and incision sites. Too many injections can distort contours or cause tachycardia or high blood pressure. Therefore, over-injection should be avoided.

Sterilization

Povidone iodine is often used for sterilization. While cleaning the patient's face, care should be taken not to get povidone iodine into his eyes. Nose hairs can be cleaned with a number 15 scalpel without covering and cleaning the patient. Some surgeons trim the nose hair after the patient is cleaned and draped. If the nose hair is to be cleaned, it is appropriate to clean

the nostrils with povidone iodine before and after cleaning. After the patient's face is wiped, it is covered with sterile drapes. Care should be taken to keep the face uncovered while covering the patient. The forehead and chin should be covered so that the tip remains open. The more open the face, the easier it is to evaluate the harmony of the nose with the face**.**

Incision

The difference between closed rhinoplasty and open technique is that there is no transcolumellar incision (Tebbetts, 2006). The advantage of the open technique compared to the closed technique is that it has a larger field of view (Foda, 2003). The medial middle and lateral crura can be evaluated in their anatomical positions (Burke & Cook, 2000). A hemitransfiction or transfiction incision can be used to reach the septum. The hemitransfiction incision is made approximately 2 mm from the caudal septum. The transfiction incision is made as a full-thickness incision through the membranous septum. In closed rhinoplasty, it is started with a marginal incision, the dorsum is reached with an intercartilaginous incision, and the septum is reached with hemitransfiction or transfiction incisions. In closed rhinoplasty, it is essential to use a head lamp that provides strong illumination to provide a good visual angle. Head lamps are charged and plug-in types. Plug-in corded lamps can limit the surgeon's movement. It is more comfortable to use rechargeable head lamps that give strong light. With marginal incisions, the lateral and medial crus are exposed, then the dorsum of the nose can be reached from the anterior septal angle. An incision is made from the anterior septal angle with the help of scissors, and then the dorsum is elevated with the help of an elevator and scissors. While elevating the dorsum, the elevation should be in the plane of the sub SMAS (superficial muscular aponeurotic system). Some surgeons also want to work in the subperichondrial plane in the dorsum. If the elevation is desired to be done with scissors, a scissor with a curved tip should be used, and the tip of the scissors should be used facing the cartilage. Otherwise, the tip of the scissors may come off the skin. It should be as deep as possible. With the help of scissors and an elevator, the dorsum elevation is completed and the dorsum should be elevated up to the radix. Periosteal elevator should be used when it comes to the bony roof in the dorsum. The nasal bone should be elevated subperiosteally. If subperiosteal elevation is not performed, postoperative swelling and bruising will be excessive. If subperiosteal elevation is performed, the postoperative recovery process is also accelerated. The tissue should be respected at every stage of the surgery,

should be worked in the right plan and excessive force should not be applied to the tissues.

Elevation

The next step after incision is elevation. Since the elevation is higher in the open technique compared to the closed technique, postoperative edema is higher, which also delays postoperative recovery. In the closed technique, there is no risk of scarring in the columella, and it can be said that postoperative recovery is faster (Bagheri et al., 2012; Rettinger, 2008). After making a marginal incision, the lateral crus and medial crus are elevated with scissors or an elevator. It is safest to use the blunt end of the elevator during elevation. If the lateral or medial crus is not elevated enough, it should not be pulled. They may break uncontrollably. Good and correct retraction is essential for good elevation. Excessive retraction should also be avoided, which can cause the cartilage to break uncontrollably. Some surgeons particularly want to dissect the lateral crus in the subperichondrial plane. In order to fully reveal the lateral and medial crus, it is necessary to extend the incision inferiorly to the footplates of the medial crus. When both lateral and medial crus are elevated, dorsum elevation is initiated. An inter-cartilaginous incision or anterior septal angle can be used to elevate the dorsum. Dorsum elevation should be in the sub SMAS plane. Some surgeons also dissect the cartilaginous roof in the subperichondrial plane. When the elevation is in line with the nasal bone, elevation should be continued subperiosteally with a periosteal elevator. Elevation to the radix should be completed. After elevation of the dorsum, an incision is made into the septum with a hemitransfiction or transfiction incision. The septum should be elevated in the subperichondrial plane. The septal cartilage is bluish whitish in color and appears exactly in this color in the subperichondrial plane. The elevator, on the other hand, moves smoothly as if sliding on an ice rink. The cranial part of the septum is formed by the perpendicular lamina of the ethmoid bone. It is elevated in the sub-periosteal plane in the bony septum. One end of the septum elevators is sharp and the other end is blunt. The blunt tip is used for sharp elevation to enter the subperichondrial plane. If the elevation is continued with a sharp tip, unwanted incisions may occur in the septum cartilage. After the cartilage septum and bone septum are elevated, the maxillary crest, which forms the septum floor, is elevated. The mucoperichondrial flap is most detached during floor elevation. In order to avoid discharge, the periosteum above the maxillary crest should be

incised with a size 15 scalpel before elevating the base and work in the subperiosteal plane.

Resection

After the incision and elevation comes the resection step. Asymmetries that cause deformity in the radix, bone dorsum, cartilage dorsum, and tip region of the nose, excess tissues are excised in the planned direction and then reconstructed. Sometimes it is possible to perform reconstruction, especially with sutures, without the need for excision. If the patient also has breathing problems, septoplasty is performed if there is a deviation of the septum. If there is turbinate hypertrophy, the turbinates are reduced by radiofrequency or endoscopic inferior turbinate reduction. According to the need, cartilage grafts are taken from the septum. In the next section, the reconstruction of each section is described in more detail separately.

Radix

Radix-related problems are usually related to the radix being higher or lower than the normal plane. The radix forms the nasofrontal angle. High radix causes masculine appearance in women. It causes the nose to be perceived as longer and larger than it is. In males, it causes a mongoloid facial (avatar face) expression. If the radix is high and it is desired to be lowered, a radix file can be used. The rasp tip of the piezzo device can be used. If the radix is low, crushed cartilage can be filled with grafts and soft tissues. This is usually done towards the end of the surgery to prevent the grafts from slipping out of place.

Nasal Dorsum

The dorsum of the nose consists of bone and cartilage. The dorsum of the bone and the dorsum of the nasal bone cartilage form the upper lateral cartilages. The upper lateral cartilages fuse with the septum in the midline. There may be humps, asymmetries or collapses called saddle nose deformity in the nasal dorsum. Bone hump is usually corrected with a rasp. If bone and cartilage hump block is desired, median osteotomies can be used. It is more difficult to take it as a block in closed rhinoplasty compared to the open technique. The safest is to straighten the dorsum of the bone with a rasp. The upper lateral cartilages form the cartilage part of the nasal dorsum, and the upper lateral cartilages merge with the septum in the midline. If there is cartilage hump, it can be removed as a block, but it is safest to separate the

upper lateral cartilages from the septum and remove the septal hump and the excess of the upper lateral cartilages separately. The use of spreader grafts and flaps in primary rhinoplasty has become much more common (Toriumi, 1995; Constantian & Clardy, 1996). When performing hump resection from the dorsum, less resection should be performed than planned, and the dorsum should be reduced step by step in a controlled manner. If over-resection is performed, it is necessary to reconstruct the over-removed areas. Irregularities may occur on the nasal dorsum. In some noses, the hump may be asymmetrical. In asymmetric noses, surgery should be done asymmetrically, and resection should not be done at the same rate from every place. The point to focus on is to obtain a flat and desired level dorsum after resection. When the nasal dorsum is brought to the desired level, the cartilage roof is reconstructed with spreader grafts or flaps. Reconstriction is performed after osteotomy in order not to dislodge the placed grafts and not to loosen the sutures. In patients with cartilage hump, the septum and upper lateral cartilages are separated from each other and the septal hump is excised. The hump-forming excesses of the upper lateral cartilages, namely the spreader flaps, are curved towards the septum and sutured to the septum. The other method is to place the spreader grafts taken from the septum between the septum and the upper lateral cartilages after removing the excess upper lateral cartilages and septal hump. The purpose of placing spreader grafts or flaps is to prevent reverse V deformity. In asymmetric noses with axis curvature, more spreader grafts can be placed on one side according to the need. Placed spreader grafts or spreader flaps are sutured with absorbable sutures. Generally, 5.0 or 6.0 polydiaxanone (PDS) sutures are used. These sutures dissolve in about 6 months.

Septum

A straight nose cannot be achieved without creating a straight septum. It is not possible to correct the tip of the nose without correcting the caudal deviations and luxations. If the patient has a complaint of nasal congestion and there is a deviation of the septum, the deviation should be corrected first. The septum cartilage may need to be used for grafting. Therefore, care should be taken not to break the septum cartilage while correcting the deviation. Septum cartilage should be removed so that it can be used as a graft. If there is deviation or luxation in the caudal septum, it should be corrected. If the caudal septum is weak, it should be supported with grafts. The L strut should be preserved so that the tip of the nose does not collapse, the type does not fall and there is no saddle nose deformity. At least 1 cm of

remnant septum should be left 1 cm caudal under the dorsum. If the septum is separated from the anterior nasal spin, it should be sutured. Some surgeons prefer absorbable sutures (4.0-5.0 PDS) for suturing, while others prefer non-absorbable sutures (4.0 -5.0 prolene). If the nose is to be shortened, 1.2 mm excision can be made from the caudal septum. After excision, excess mucoperichondrial flap may occur. If necessary, excision can be made from the flap. If the septum is to be sutured to the anterior nasal spine (ANS), care should be taken to ensure that the ANS is in the midline. Asymmetric noses may not be in the midline. In this case, spinoplasty can be performed. With the help of the round, the spin can be corrected by rounding.

Osteotomy

It is usually done after the bone and cartilage hump is removed and septoplasty is done. Osteotomy is done to close the open roof or to correct the axis curvature. In order to reduce bleeding, different agents are used to provide controlled hypotension in rhinoplasty surgery (Vahabi et al., 2018; Tuncel et al., 2013; Srivastava et al., 2013). It can be done internally or externally (percutaneously). Osteotomies are named differently depending on where they are made. Lateral osteotomy; It is made on the lateral walls of the nasal bone. It can be done internally with an osteotome or externally with a 2 mm chisel. It is also possible to do it with piezzo or electric saw. It can be done as low to low if the radix area of the patient is wide, and low to high if the radix area is not desired to be narrowed too much. Infrafraction is created by breaking the bony side walls inward. If desired, out fracture can also be created. If the axis is in the midline, bilateral infrared infraction is created. If the axis is not in the midline, infrafraction can be performed on one side and out fracture on the other side to bring the axis to the midline. The out-fractured side is the side where the axis is curved. In patients with a very curved axis, lateral osteotomy is performed at two different levels on the side where the axis is not curved, this is called double osteotomy. For example, if the axis is curved to the right, double osteotomy to the right can be performed, and outfracture to the left. The upper limit of the lateral osteotomy is at the medial canthus level, and this level should not be exceeded. Transverse osteotomy; It is an osteotomy performed on the right and left lateral of the radix to the nasal lateral wall at the level of the radix. This osteotomy is combined with the lateral osteotomy. It can be done percutaneously with a 2 mm chisel or internally with a 90-degree saw. Radix osteotomy; It is done to reduce the radix. It is done percutaneously with 1 mm or 2 mm chisel. Paramedian osteotomy; It is made from the cartilage

and bone roof junction, from the right and left lateral of the K point. A 2.3.4 mm chisellar can be used. If it is done right in the midline, the median osteotomy is called paramedian osteotomy if it is made a little laterally from the midline. This osteotomy merges with the transverse osteotomy at the radix level. Saw or piezzo can be used instead of chisel.

Tip

Tip reconstruction is done after dorsum, septoplasty and osteotomies. In closed rhinoplasty, both domes are removed from the nostril. The location of the desired new dome is determined by bringing both domes side by side with the help of collet. It is marked with a marker pen. It is necessary to pull both domes equally, otherwise asymmetries may occur when they are sutured. If the tip of the nose is large and it is desired to be reduced, excision can be made from the lateral crus. Care should be taken to ensure that both lateral crus are equal after excision. If the tip is to be raised, Gruber's suture and hemitransdomal sutures are removed from the new dome points determined during traction. In the supratip region, the pitangu ligament is dissected from the middle of the nose, and a window is opened, and one hemi dome is removed from the other nostril. Thus, both hemi domes can be combined with inter-domal sutures. Domes that are sutured together are placed in the nose. When the dome complex is placed inside the nose, how the tip appears and its size is evaluated. In open surgery, the columella must be sutured to make a complete evaluation. If it is desired to increase the height of the tip, lateral crural ringing can be increased or a cap graft can be placed. If the projection is good and the rotation is high, medial crural overlap can be done. The biggest difficulty in creating the tip in closed rhinoplasty is pulling both hemi-domes equally and suturing them symmetrically to each other. Another difficulty is to extract both domes from the same nostril. After the inter-domal sutures are placed, the columellar strut is placed. The majority of surgeons prefer absorbable sutures in the dome area. Generally, 5.0 and 6.0 PDS sutures are used. After the columellar strut is placed, the cap graft can be placed. 5.0 or 6.0 PDS is used in the cap graft.

Control

Surgical steps in closed rhinoplasty are adjustment of the radix level, correction of the bone dorsum if there is hump, cartilage roof hump resection, upper lateral cartilages and septal hump separately, septoplasty, osteotomies, reconstruction of the cartilage roof and tip surgery. After each

step is carefully passed and the tip complex is placed in the nose, radix dorsum and dorsum tip transitions are checked. If there is an axis curvature, it is checked whether the axis is in the midline. If there are any irregularities, it is checked. If the grafts are palpable, camouflage grafts are placed. When you are sure of everything, it is switched to shutdown. Hemitransfixation or tension incisions are sutured with 6.0 vicryl or rapid vicryl. It is sutured in the same way as for marginal incisions.

Fixation

If it is not desired to put a tampon in the septum, the septum can be sutured in the inferior superior plane and transseptally from cranial to caudal. 4.0 or 5.0 vicril can be used as suture material. However, placing a silicone tampon increases intranasal support. The size of the tampon can be adjusted and reduced according to the patient. Some surgeons insert a drain into the lateral osteotomy line after a silicone pad is placed in the nose. After the tampon process, the outer surface of the nose is washed with physiological saline. After drying, taping is done and a thermal splint, the size of which is adjusted according to the patient's nose, is placed. Silicone splint inside the nose in 2-5 days. Thermal splint is removed after 7-10 days.

Postoperative Care

After the patient comes out of the operation, he is laid down with his head elevated about 30 degrees. The mattress is lifted 30 degrees from the waist. Cold application is made for the first 24 hours. Cold application reduces pain, edema and bruises. Care should be taken not to put the cold compress on the nose while applying cold. A cold compress should be placed on the cheeks and forehead. After the operation, the patient may have abdominal pain due to swallowing the blood leaking from the posterior, and if necessary, a proton pump inhibitor is given. Analgesics and antibiotics are started.

CONCLUSION

Closed rhinoplasty and open rhinoplasty are not alternative surgeries. While some surgeons perform all their operations open, some perform both closed and open operations, while others perform all operations closed, including revision. Here the choice is your surgeon. More important than the closed or open approach is to get good results. Some surgeons prefer that approach because they get better results when they are closed, while others prefer that approach because they get better results when they are open. The

advantage of closed rhinoplasty is the absence of a transcolumellar incision and possible scarring. One of the difficulties of this surgery is the narrower angle of view and the reconstruction in a narrow area.

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CLAVICLE FRACTURES: CURRENT CONCEPTS

Eşref SELÇUK

- Affiliation: Trakya University Department of Orthopedics and Traumatology, Edirne/TURKIYE
- ORCID: 0000-0002-1657-1110
- Mail: trkesref@hotmail.com

Cihan ÜNYILMAZ

- Affiliation:Trakya University Department of Orthopedics and Traumatology, Edirne/TURKIYE
- ORCID: 0000-0001-9130-4365
- Mail: cihanunyilmaz@trakya.edu.tr

INTRODUCTION

Clavicle fractures are a commonly encountered orthopedic injury, comprising approximately 3% of adult fractures and accounting for 35% of injuries around the shoulder (Postacchini et al., 2010; Robinson, 1998). While they can occur at any age, they are more prevalent in young adults and adolescents due to their active lifestyles and participation in sports or physical activities (Nordqvist & Petersson, 1994).

The clavicle is a long bone that bridges the axial and appendicular skeletal systems, providing stability and support to the shoulder joint. Clavicle fractures can result from various mechanisms, including direct trauma, falling onto an outstretched arm, or high-energy accidents (motor vehicle accidents or contact sports) (Allman, 1967).

Accurate diagnosis, classification, and management of clavicle fractures are crucial for achieving favorable patient outcomes

Anatomy & Physiology

Comprehensive anatomy and physiology of the clavicle and its surrounding structures is necessary for the evaluation of potential injuries that may arise from clavicle fractures. Knowledge of the neural, vascular, and soft tissue structures around the clavicle, as well as their impact on shoulder movement, is essential for proper treatment planning.

Anatomy of the Clavicle and its Surrounding Structures

Neural Structures

Among the important neural structures around the clavicle, the brachial plexus is formed by the anterior rami of the C5 to T1 cervical spinal nerves.

Vascular Structures

The subclavian artery and vein are important vascular structures in the clavicle region. These vessels are responsible for supplying blood to the upper extremity and facilitating the return of blood from the upper extremity.

Soft Tissue Structures

The clavicle serves as a connection site for various ligaments and muscles, including the sternoclavicular and acromioclavicular ligaments, as well as muscles such as the sternocleidomastoid, trapezius, and pectoralis major. The coracoclavicular ligament provides a connection between the

coracoid and clavicle. The coracoclavicular lig. consists of the conoid and trapezoid ligaments (Figure 1). Damage to the ligaments accompanying a clavicle fracture can change the choice of treatment.

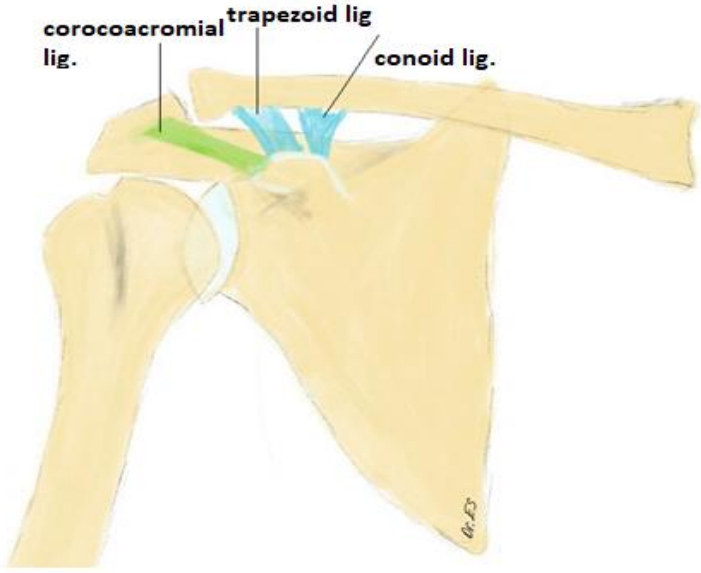

Figure 1. Coracoacromial, Trapezoid, and Conoid Ligaments

Potential Injuries

Neurovascular Injury

Due to the proximity of the brachial plexus and subclavian vessels to the clavicle, fractures can result in injuries to these structures, leading to complications such as nerve deficits, vascular insufficiency, or bleeding.

Soft Tissue Injury

Clavicle fractures can also cause damage to the surrounding ligaments and muscles, resulting in pain, instability, or impaired shoulder function.

Physiology of Shoulder Movement

The clavicle has a vital role in the physiology of shoulder movement by providing stability and support for the clavicle, and scapula. It acts as a bridge between the sternum and scapula, allowing for a wide range of movements in the shoulder girdle, including elevation, depression, protraction, and retraction. Clavicle fractures can disrupt the biomechanics of the shoulder, leading to pain, weakness, or limited range of motion, which may require treatment to restore normal shoulder function.

Histology

The histological characteristics of the clavicle can influence the formation of fractures and subsequent treatment.

Histological Characteristics of the Clavicle

Cortical Bone

The clavicle is predominantly composed of cortical bone, which provides structural support and contributes to the overall strength of the bone (Kihlström et al., 2017).

Trabecular Bone

The trabecular bone is primarily located at the medial and lateral ends. This spongy bone plays a role in load distribution and energy absorption, which can influence the observed fracture patterns (Kihlström et al., 2017).

The Effect of Histological Characteristics on Fracture Formation

Bone Composition

The ratio of cortical to trabecular bone in the clavicle can influence its susceptibility to fractures. Cortical bone provides hardness and strength, while trabecular bone contributes to energy absorption during impacts (Kihlström et al., 2017). In clavicle fractures, the proportions of cortical and trabecular bone can affect the risk and pattern of fractures. Generally, a higher proportion of cortical bone is associated with increased hardness, but it reduces the ability to absorb energy during traumatic impacts, potentially resulting in a higher risk of fractures under high-energy trauma. Conversely, a higher proportion of trabecular bone can absorb more energy during impacts and potentially reduce the risk of fractures under low-energy impacts (Kihlström et al., 2017). However, susceptibility to fractures is also significantly influenced by other factors such as the direction and magnitude of impact force, loading rate, bone mineral density, microarchitecture, and bone remodeling rate, which collectively determine the overall bone quality (Bouxsein et al., 2010). Furthermore, osteoporosis in the proportions and properties of cortical and trabecular bone can also impact fracture risk. For instance, aging is associated with cortical thinning and disruption of the trabecular network, which can increase the risk of fractures (Bouxsein, 2003).

Bone Morphology

The S-shaped curvature and the distribution of cortical and trabecular bone contribute to its biomechanical properties, which can influence the location and shape of fractures (Kihlström et al., 2017).

Treatment Implications

Bone Healing

The histological characteristics of bone, such as the presence of trabecular bone at the medial and lateral ends, can influence healing potential of fractures. Understanding these characteristics can guide treatment decisions, such as the choice between conservative and surgical management (Kihlström et al., 2017).

Fracture Fixation

The properties of cortical and trabecular bone can influence the stability and fixation of fracture fragments during the surgical treatment. Having sufficient knowledge about the histological characteristics of the clavicle can help ensure the use of appropriate fixation techniques (Kihlström et al., 2017).

Fracture Mechanism

Trauma Types

Direct Trauma

Direct blows to the clavicle, such as those experienced during sports activities, motor vehicle accidents, or falls, are cause of clavicle fractures (Postacchini et al., 2002; Nordqvist and Petersson, 1994).

Indirect trauma

Indirect forces transmitted through the upper extremity, such as falling onto an outstretched hand, can also result in clavicle fractures (Nordqvist and Petersson, 1994).

Fracture Types

Middle 1/3 Fracture

Fractures of the middle third of the clavicle, which account for approximately 80% of all clavicle fractures, commonly result from direct trauma (Postacchini et al., 2002; Robinson, 1998).

Lateral 1/3 Fracture

Fractures in the lateral one-third of the clavicle are often accompanied by injuries to the acromioclavicular joint, coracoclavicular ligaments, or adjacent soft tissues (Robinson, 1998).

Medial 1/3 Fracture

Fractures occurring in the medial one-third of the clavicle are relatively uncommon, accounting for approximately 2-3% of all clavicle fractures (Robinson, 1998). These fractures are typically associated with high-energy mechanisms.

The characteristics of the fracture

Displacement

The fragment may be displaced or undisplaced depending on the degree of separation (Robinson, 1998).

Fragmentation

The presence of multiple fracture fragments or fragmentation can complicate the management of clavicle fractures and may require surgical intervention (Robinson, 1998).

Diagnosis and Imaging

The initial step in diagnosing clavicle fractures involves conducting a thorough medical history and physical examination. This is followed by conducting relevant imaging tests to confirm the diagnosis, evaluate the severity of the injury, and assist in determining the appropriate course of treatment.

Physical Examination

During the physical examination, the clinician should look for signs of a clavicle fracture, such as swelling, bruising, or deformity over the clavicle. Tenderness and restricted movement in the affected shoulder may be observed through palpation along the length of the clavicle due to pain (Postacchini et al., 2002). Evaluation and documentation of the neurovascular condition, including sensory, motor function, and peripheral pulses, are necessary (Zlowodzki et al., 2005).

Radiographic Imaging

Radiographic imaging is crucial for confirming the diagnosis of a clavicle fracture and determining the fracture pattern and degree of displacement

(Figure 2). The following radiographs are commonly obtained for suspected clavicle fractures:

•Anteroposterior (AP) view of the clavicle: This standard view helps visualize the fracture site, alignment, and any associated displacement (Zlowodzki et al., 2005).

•15-30° cephalic tilt view (Zanca view): This view allows for better visualization of lateral 1/3 of clavicle and associated acromioclavicular joint injuries (Zlowodzki et al., 2005).

•Serendipity view (40° cephalic tilt view): This angled view is particularly useful for imaging the medial clavicle and sternoclavicular joint and identifying fractures that may be hidden in other views.

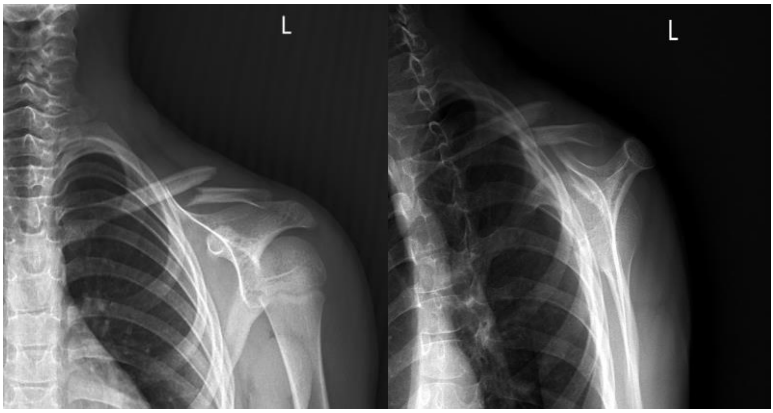

Figure 2. Left clavicle fracture shoulder AP and scapula Y radiographs.

Other imaging methods

Magnetic resonance imaging (MRI) and computed tomography (CT) can be used in the following cases:

• CT scan: It is useful for evaluating complex or fragmented fractures, assessing the relationship between fracture fragments, and planning surgical intervention.

• MRI: It is used to evaluate associated soft tissue injuries (ligament or tendon injuries) or to assess the presence of a suspected brachial plexus injury

Treatment

The decision between surgical and non-surgical (conservative) treatment options for clavicle fractures is based on various factors, including the type of fracture, degree of displacement, patient-related factors, and the

potential risks and benefits associated with each approach. Generally, uncomplicated fractures are initially managed conservatively using slings, immobilization, and physical therapy (Hill et al., 1997). However, complex cases involving significant displacement, fragmentation, or associated injuries may necessitate surgical intervention (Zlowodzki et al., 2005). Fracture classifications such as the Allman and AO/OTA classification systems can provide guidance for the most appropriate treatment approach (Allman, 1967; Müller et al., 1990).

A. AllmanClassification:

Group I: Medial 1/3 (proximal) clavicle fractures

Conservative treatment is generally recommended for minimally displaced or stable fractures (Robinson, 2004).

Surgical intervention may be considered for significantly displaced fractures or those with neurovascular or soft tissue risks (Robinson, 2004).

Group II: Midshaft (middle) 1/3 clavicle fractures

Conservative treatment is typically the first choice for minimally displaced or stable fractures (Canadian Orthopaedic Trauma Society, 2007). Surgical intervention may be indicated for significantly displaced or fragmented fractures, shortened fractures, or those at high risk of nonunion or malunion (Canadian Orthopaedic Trauma Society, 2007). If surgery is planned for these types of fractures, the gold standard treatment method is open reduction and internal fixation.

Group III: Lateral 1/3 (distal) clavicle fractures

Conservative treatment is typically recommended for minimally displaced and stable fractures with a intact coracoclavicular ligament (Robinson, 2004). Surgical intervention may be necessary for significantly displaced fractures or associated ligamentous injuries such as acromioclavicular joint dislocations (Robinson, 2004).

B. AO/OTA Classification:

Type A: Simple fractures

Conservative treatment is generally recommended for minimally displaced or stable fractures (Smekal et al., 2009). Surgical intervention may be considered for significantly displaced or unstable fractures (Smekal et al., 2009).

Type B: Wedge fractures

Conservative treatment is typically recommended for minimally displaced or stable fractures (Smekal et al., 2009). Surgical intervention may be necessary for significantly displaced or unstable fractures or those with associated soft tissue risks (Smekal et al., 2009).

Type C: Comminuted fractures

Surgical intervention is typically recommended for clavicle fractures that exhibit significant displacement or fragmentation, as well as fractures with a high risk of nonunion or malunion (Smekal et al., 2009).

C. Neer Classification (lateral clavicle fractures)

Type 1: These are extra-articular fractures. The fracture occurs lateral to the coracoclavicular (CC) ligaments. They are stable fractures and are treated conservatively.

Type 2A: The fracture occurs medial to the CC ligaments. The CC ligaments are intact. There is medial displacement, and these are unstable fractures. Nonunion rates are high with conservative treatment, and surgical treatment is preferred.

Type 2B: The fracture line is between the CC ligaments, and the conoid ligament is torn. In another variant, the fracture line is lateral to the CC ligament, and both the conoid and trapezoid ligaments are torn. There is significant medial displacement, and nonunion rates are high with conservative treatment. These are unstable fractures, and surgical treatment is preferred.

Type 3: These are intra-articular fractures. The CC ligaments are intact. They are stable fractures, and conservative treatment is preferred.

Type 4: These are physeal injuries seen in patients with an immature skeletal system. The CC ligaments are intact. They are stable fractures, and conservative treatment is applied.

Type 5: These are unstable fractures accompanied by a comminuted fracture. The CC ligaments are intact. Surgical treatment is preferred.

In certain cases, conservative treatment may be considered, taking into account the patient's overall health condition and the stability of the fracture (Smekal et al., 2009).

Conservative Treatment

For clavicle fractures, conservative treatment is typically the initial approach, especially for minimally displaced or stable fractures. The main objectives of conservative treatment are to alleviate pain, preserve shoulder function, and promote fracture healing, all while avoiding potential complications associated with surgery (Robinson, 2004). However, it's important to note that in cases where there is a significant shortening of more than 2 cm or greater than 10%, conservative treatment may result in suboptimal clinical outcomes and an increased risk of developing glenohumeral joint arthritis (Hoogervorst et al., 2018).

The following conservative treatment options are commonly employed for clavicle fractures:

Arm Sling or Shoulder Immobilizer

The use of an arm sling or shoulder immobilizer is the most common conservative treatment for clavicle fractures (Figure 3). These devices provide support and immobilization to the affected limb, allowing the fracture site to remain stable and promote healing (Smekal et al., 2009). The duration of immobilization typically ranges from 2 to 6 weeks, depending on the severity of the fracture and the patient's healing capacity (Hill et al., 1997).

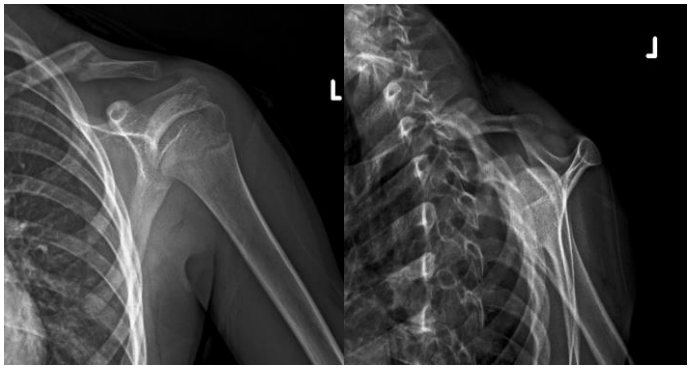

Figure 3. Clavicle fracture at 4 months after conservative treatment.

Pain management

Pain relief is an important component of conservative treatment, and it can be achieved through the use of oral analgesics such as acetaminophen and opioids, depending on the severity of the pain and the patient's tolerance.

Surgical Treatment

Surgical treatment options for clavicle fractures have evolved over time with the goal of achieving optimal fracture healing and restoration of shoulder

function. The decision to perform surgery depends on factors such as the fracture type, displacement, patient's age, activity level, and presence of associated injuries (Table 1) (Robinson, 2004). There is no specific cut-off value that determines definitively which patients will benefit from surgical treatment (Hoogervorst et al., 2018). Common surgical options are utilized in fractures where there is shortening and disruption of shoulder and scapular kinematics.

Table 1. Relative Surgical Indications for Clavicle Shaft Fractures

Fracture related	**Additional injury**	**Patient related**
• More than 2 cm displacement • Shortening of 2 cm or more than 10% • Comminuted fracture • Segmental fracture • Open fracture	• Neurovascular injury • Floating shoulder • Additional upper extremity fracture	• Polytrauma •Elite/professional athlete

Open Reduction and Internal Fixation (ORIF)

Open Reduction and Internal Fixation (ORIF) is a commonly used surgical technique for the treatment of displaced clavicle fractures. It involves repositioning the fractured bone segments and stabilizing the fracture site using plates and screws (Canadian Orthopaedic Trauma Society, 2007). The primary advantage of ORIF is the direct visualization of the fracture site, allowing for accurate reduction and alignment of the bone segments. Incisions should be carefully made, considering the subcutaneous position of the clavicle and proximity to important neurovascular structures.

There are two main approaches for ORIF: anterior plating and anterior-superior plating. Anterior plating is typically used for midshaft fractures, while anterior-superior plating can be used for distal third fractures (Hill et al., 2017). Each approach has its own advantages and disadvantages. Anterior-superior plating provides better biomechanical stability, but carries a higher risk of hardware irritation due to the subcutaneous position of the plate. İnsizyon yerleşiminin seçimi, kırık konumuna ve tercih edilen plak pozisyonuna (anterior veya superior) bağlıdır (Lui ve ark 2017). Kesi uzunluğu değişebilir, ancak kırık parçalarının doğrudan görüntülenmesine ve manipülasyonuna izin vermek için yeterli olmalıdır.

The clavicle is a subcutaneous bone with minimal soft tissue coverage, and care must be taken to protect the underlying structures. This includes the platysma muscle, which is usually incised at the same level as the skin incision. Deeper dissection requires careful identification and preservation of the supraclavicular nerves, which extend into the depths of the platysma and may be at risk during the procedure. Additionally, the infraclavicular neurovascular bundle (which includes the axillary artery and vein along with the cords of the brachial plexus) is located medial and inferior to the clavicle and should be preserved (Ropars et al., 2017). During wound closure, attention should be paid to layered closure, with care taken to reapproximate the platysma muscle. This not only provides a more cosmetic closure but also reduces the risk of postoperative complications such as wound dehiscence and infection.

Compression plating utilizes the principles of compression applied through the plate to provide stability and support fracture healing (Figure 4-5). Additionally, a compression screw can be placed through the plate and into the bone, compressing the fracture fragments together. This method provides strong fixation but is generally not suitable for comminuted fractures (Zlowodzki et al., 2005). Lag screw and neutralization plating are alternative methods that can be used when compression plating is not appropriate.

The lag screw provides interfragmentary compression, and the plate neutralizes the forces acting on the screw, preventing it from failing. Bridge plating is typically used in cases where direct manipulation of fracture fragments may cause further damage, often seen in comminuted fractures (Figure 5-6).This method involves fixation of the plate to the bone fragments, bridging the fracture site, and allowing for secondary bone healing (Zlowodzki et al., 2005).

Commonly used plate types in ORIF include dynamic compression plates, limited contact dynamic compression plates, and locking compression plates. The choice of the plate depends on the type and location of the fracture and the surgeon's preference.

Potential complications associated with ORIF include infection, hardware irritation, nonunion, and malunion (Woltz et al., 2017).

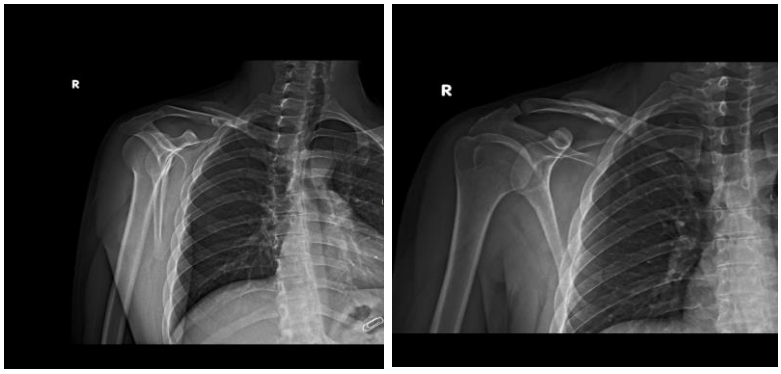

Figure 4. Preoperative X-ray image

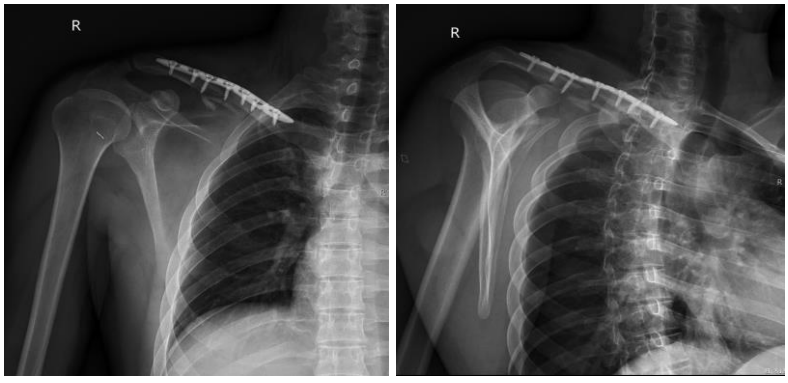

Figure 5. Postoperative open reduction internal fixation(compression plating)

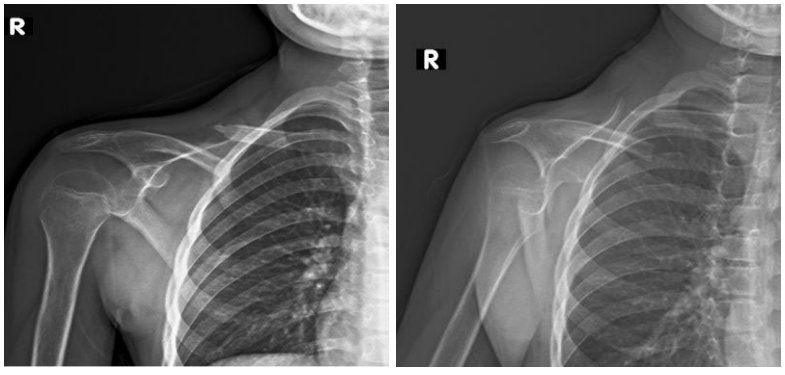

Figure 6. Preoperative radiograph of right clavicle fracture

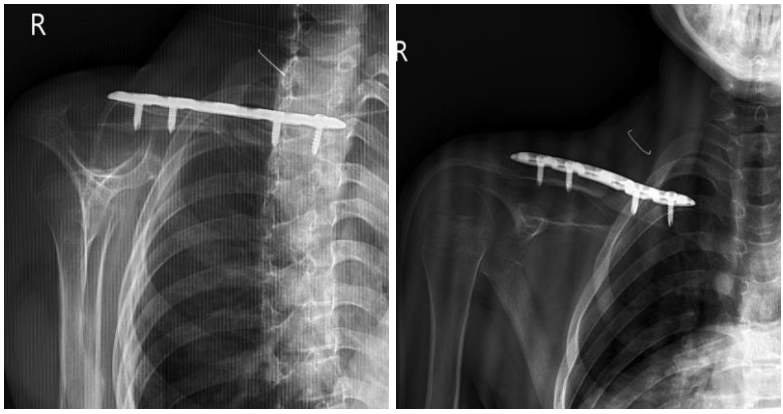

Figure 7. Postoperative open reduction internal fixation (bridge plating)

Intramedullary Fixation

Intramedullary fixation is another surgical technique used in the treatment of clavicle fractures. This technique involves the insertion of a rod or nail into the medullary canal of the clavicle, starting from the sternoclavicular joint end (Jubel et al., 2003). This method has the advantage of being less invasive compared to ORIF and may result in smaller surgical incisions. However, intramedullary fixation may be less suitable for certain fracture patterns and carries risks such as material migration, nonunion, and malunion. Additionally, secondary shortening and telescoping may be observed in these patients. It should be noted that applications such as Titanium Elastic Nailing (TEN) provide fracture alignment but do not provide fracture fixation. In patients treated with TEN, secondary surgical intervention rates ranging from 0% to 36% have been reported (Braunv et al., 2014; Hoogervorst et al., 2018).

In a study published by R. Stichhauer et al. in 2022, titanium elastic nails were applied to 20% of 696 pediatric patients. It was observed that patients who underwent surgery discontinued the use of shoulder immobilizers and similar adjunctive materials earlier, but there was no significant difference in terms of complete recovery.

The entry point of the nail is typically at the medial end of the clavicle, aligned with the long axis of the bone. It is important to ensure that the entry point is properly placed to avoid damage to surrounding soft tissues and to ensure accurate positioning of the nail within the medullary canal.

After the nail is inserted, it is important to verify its position using fluoroscopy to ensure proper placement and sufficient reduction of the

fracture. After the surgery, leaving the nail slightly protruding from the entry point can facilitate its removal after the fracture has healed. However, this may cause discomfort and skin irritation, and some surgeons prefer to cut the nail flush with the bone surface and, if necessary, remove it in a separate surgical procedure (Jubel et al., 2003).

Minimal Invasive Plate Osteosynthesis (MIPO)

Minimal Invasive Plate Osteosynthesis (MIPO) is a technique that combines the benefits of both ORIF and intramedullary fixation. It involves using small incisions to place a plate along the clavicle, which is then fixed with screws (Zlowodzki et al., 2005). The main advantage of MIPO is the minimal soft tissue dissection, which can reduce the risk of complications such as infection and material irritation. However, MIPO may not be suitable for all fracture patterns and carries the risk of nonunion and malunion (Zlowodzki et al., 2005).

Surgical complications that may be associated with these treatment options include infection, material-related issues (such as irritation or migration), nonunion, malunion, nerve or vascular injury, and delayed fracture healing (Woltz et al., 2017). The surgeon performing the treatment will consider these factors when selecting the most appropriate surgical technique for each patient.

Different types of plates, such as hook plates, straight plates, and anatomical plates, can be used depending on the shape of the clavicular fracture (Figure 8-9).

Figure 8. Examples of clavicle plates

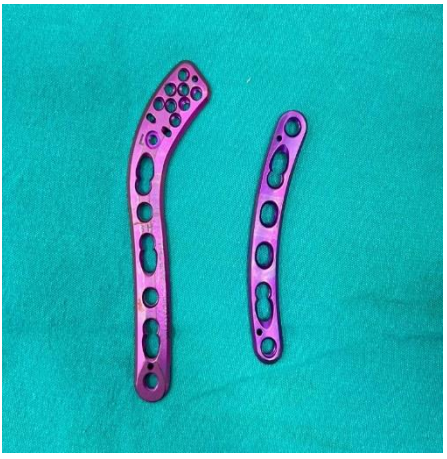

Figure 9. Examples of clavicle plates

Multiple studies have shown that there is no significant difference in clinical and functional outcomes between open reduction-internal fixation and conservative treatment in the medium and long term. However, a lower rate of nonunion has been observed in the operative groups. In young and active patients, surgical treatment may be recommended to enable a quicker return to daily activities (Micheloni et al., 2019; Štichhauer et al., 2022).

When determining the treatment option, the advantages and disadvantages of conservative and surgical treatment should be explained to the patient. Taking into account the patient's existing comorbidities, age, occupation, and social life, the final treatment option should be decided collaboratively.

Complications

Nonunion

Nonunion refers to the failure of a fracture to heal within the expected timeframe, typically around 6 months after injury or surgery (Wiesel & Delahay, 2010). Nonunion is a potential complication of clavicle fractures and can lead to persistent pain, functional impairment, and the need for additional surgical intervention. The incidence of nonunion following clavicle fracture treatment varies depending on the chosen treatment method and patient factors, with higher rates observed in non-surgically treated cases compared to surgical fixation (Mckee et al., 2006).

The causes of nonunion in clavicle fractures may include:

I. Inadequate immobilization or early mobilization of the fracture site, excessive movement, and disruption of the healing process.

II. Severe displacement, fragmentation, or shortening of the fracture segments that can compromise blood flow to the bone and impair healing.

III. Patient factors such as advanced age, smoking, diabetes, and use of certain medications that can adversely affect bone healing.

IV. Infection that can impede the healing process and lead to nonunion (Wiesel & Delahay, 2010; Mckee et al., 2006; Marsell & Einhorn, 2011).

The diagnosis of nonunion is based on clinical findings such as persistent pain and lack of functional improvement, as well as imaging studies such as X-rays and computed tomography (CT) scans that demonstrate the absence of bridging callus in the fracture site after an adequate healing period.

When nonunion is diagnosed, management options include:

• Conservative treatment: If nonunion is stable and minimally symptomatic, conservative measures such as activity modification, pain management, and the use of bone stimulators may be considered (Wiesel & Delahay, 2010).

• Surgical intervention: Symptomatic or unstable nonunion cases may require surgical treatment to promote bone healing. Surgical options may include debridement of the nonunion site, bone grafting, and fixation using plates, screws, or intramedullary devices (Woltz et al., 2017).

The choice of treatment for nonunion depends on the severity of the condition, the presence of complications such as infection, and the patient's overall health. The treating surgeon will determine the most appropriate management strategy for each patient..

Infection

Infection is another serious complication that can occur after clavicle fracture treatment, especially following surgical intervention. The incidence of infection varies depending on the type of surgery performed and the use of prophylactic antibiotics.

Postoperative infections can manifest as superficial skin infections or deep bone infections (osteomyelitis). Symptoms may include fever, pain, redness, swelling, purulent discharge at the surgical site, as well as delayed healing or nonunion.

Infection can be confirmed through laboratory tests such as increased white blood cell count and C-reactive protein, as well as imaging studies such as X-rays, CT scans, or MRI that show changes consistent with infection. In some cases, biopsy or aspiration may be performed to identify the causative organism and guide antibiotic treatment.

Treatment of infection following clavicle fracture surgery involves a combination of systemic antibiotics and local wound care. In severe cases, surgical debridement or removal of the material may be necessary. The choice of treatment depends on the severity of the infection, the presence of other complications, and the patient's overall health (Ferran et al., 2010).

Postoperative Follow-up

Postoperative follow-up is necessary to monitor the progress of patients who have undergone surgical treatment for clavicle fractures. The timing and recommendations for each follow-up visit may vary depending on the surgical technique used, the severity of the fracture, and individual patient factors. However, a general guideline for follow-up visits may be as follows:

First Visit (1-2 weeks post-surgery):

The initial follow-up visit is typically scheduled within 1-2 weeks after the surgery. During this visit, the surgeon evaluates the surgical site for signs of infection, assesses the healing process, and ensures that the patient's pain is well-managed. The surgeon may also provide instructions for continuing gentle range of motion exercises and the use of a sling or brace for immobilization (McKee et al., 2006).

Second Visit (4-6 weeks post-surgery):

During this follow-up visit, the surgeon assesses the patient's progress in regaining shoulder range of motion and evaluates the healing of the fracture using imaging studies such as X-rays. If the patient is making good progress, the surgeon may allow the discontinuation of the sling or splint and the initiation of active and assisted range of motion exercises under the guidance of a physical therapist (McKee et al., 2006).

Third Visit (3 months post-surgery):

By the 3-month follow-up visit, the patient should have made significant progress in regaining shoulder range of motion and strength. The surgeon evaluates the healing of the fracture and may allow further progression to strengthening exercises and functional training as part of the rehabilitation program.

Fourth Visit (6 months post-surgery):

During the 6-month follow-up, the surgeon assesses the patient's overall shoulder function, range of motion, and strength. If the patient has made satisfactory progress in rehabilitation and the fracture has sufficiently healed, they may be allowed to return to sports or other demanding activities.

Final Visit (1 year post-surgery):

The final follow-up visit is typically scheduled approximately 1 year after the surgery. During this visit, the surgeon evaluates the long-term outcomes of the surgical treatment, including shoulder function, range of motion, and strength. If the patient has fully recovered and there are no complications, the surgeon may discharge the patient without the need for further follow-up (Judd et al., 2009).

It is important to note that individual follow-up programs may vary depending on the patient's progress and any complications that may arise. The surgeon performing the treatment will determine the most appropriate follow-up program and recommendations based on the specific circumstances of each patient.

Rehabilitation

Conservative Treatment and Rehabilitation

After the acute pain has subsided and the fracture site has become stable, guided by a physical therapist, gradual range of motion and strengthening exercises can be initiated. This helps in regaining shoulder function and preventing complications such as stiffness and muscle atrophy (Smekal et al., 2009).

The advantages of conservative treatment compared to surgery include avoiding surgical complications such as infection, material irritation, migration, and anesthesia risks, as well as lower costs associated with non-surgical management (Robinson, 2004).

Disadvantages of conservative treatment may include inadequate fracture alignment, which can contribute to shoulder stiffness and functional limitations, as well as potential complications such as nonunion, malunion, and longer periods of immobilization (Canadian Orthopaedic Trauma Society, 2007).

During conservative treatment, regular follow-up visits with the treating doctor are typically scheduled to monitor the patient's progress, evaluate fracture healing using imaging studies (such as X-rays), and assess the need for any further interventions (Hill et al., 1997).

Surgical Treatment and Rehabilitation

Rehabilitation following surgical treatment of clavicle fractures is crucial for optimal recovery and regaining shoulder function. The specific rehabilitation program depends on the surgical method used (ORIF or intramedullary nailing) and the individual development of the patient. It is essential to work closely with a physical therapist to develop and adapt the program according to the patient's needs.

For both ORIF and intramedullary nailing, the initial focus is on pain and inflammation control, protecting the surgical site, and preserving range of motion in the elbow, wrist, and hand. The rehabilitation program typically progresses through several stages:

Early stage (0-2 weeks):

During this stage, the patient's arm is immobilized in a sling or brace to protect the surgical site (Mckee et al., 2006). Gentle pendulum exercises may be initiated within the first few days to maintain passive range of motion in the shoulder without exerting excessive stress on the healing fracture. Activities involving strenuous or excessive shoulder movement, such as lifting objects or reaching overhead, are generally restricted during this stage.

Patients are encouraged to perform active range of motion exercises for the elbow, wrist, and hand.

Intermediate stage (2-6 weeks):

In this stage, the sling or brace can be removed, and the patient can gradually begin active and assisted active range of motion exercises for the shoulder under the guidance of a physical therapist. The focus is on restoring shoulder mobility, and exercises may include shoulder flexion, extension, abduction, and external and internal rotation. It is important to avoid exercises that cause pain or discomfort. Heavy lifting or resistance exercises are typically not recommended during this stage (Mckee et al., 2006).

Strength-building stage (6-12 weeks):

Once the patient has regained full range of motion, the focus shifts to strengthening the shoulder muscles. Resistance exercises using elastic bands or weights can be initiated. The intensity and complexity of the exercises can be gradually increased under the supervision of a physical therapist, taking care not to exacerbate pain or discomfort. During this stage, the patient can gradually resume daily activities involving the shoulder, including light lifting. However, heavy lifting should still be avoided (Mckee et al., 2006).

Advanced stage (12 weeks and beyond):

In the advanced stage, the rehabilitation program aims to return the patient to their pre-injury level of function. This includes sport-specific exercises and functional training tailored to the patient's individual needs and goals. The patient can gradually return to heavier lifting and sports activities as tolerated under the guidance of a physical therapist.

Postoperative rehabilitation may vary depending on factors such as the severity of the fracture, the patient's age and overall health, and their activity level. Regular follow-up with the treating surgeon and physical therapist is necessary to monitor the patient's progress and make any necessary adjustments to the rehabilitation program (Judd et al., 2009).

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PEDIATRIC SUPRACONYLAR HUMERUS FRACTURES

Doğukan ERKAL

- Affiliation: Trakya University Department of Orthopedics and Traumatology, Edirne/TURKIYE
- ORCID: 0000-0001-7390-5781
- Mail: dogukanerkal@trakya.edu.tr

Murat EREM

- Affiliation: Trakya University Department of Orthopedics and Traumatology, Edirne/TURKIYE
- ORCID: 0000-0002-9743-5515
- Mail: muraterem83@hotmail.com

A) INTRODUCTION

In the elbow fractures supracondylar humerus fractures is the most common cause in children. Supracondylar humerus fractures are seen in 3 and 10 years in children frequently. It has been reported this fractures seen in non dominant limb.(Farnsworth et al., 1998) If it isn't treated properly deformity of limb inevitable.

Children often falls on outstreched arm. They protect theirselves at this position. But that protective position can't protect their neurovascular structure.

B) ANATOMY- INJURY MECHANISM

Elbow joint has a complex anatomy. With humerus, ulna and radius it has unique range of motion. Humerus afnd ulna allows flexion-extension.(**Figure 1.1**) Humerus and radius allows supination-pronation.(**Figure 1.2**)

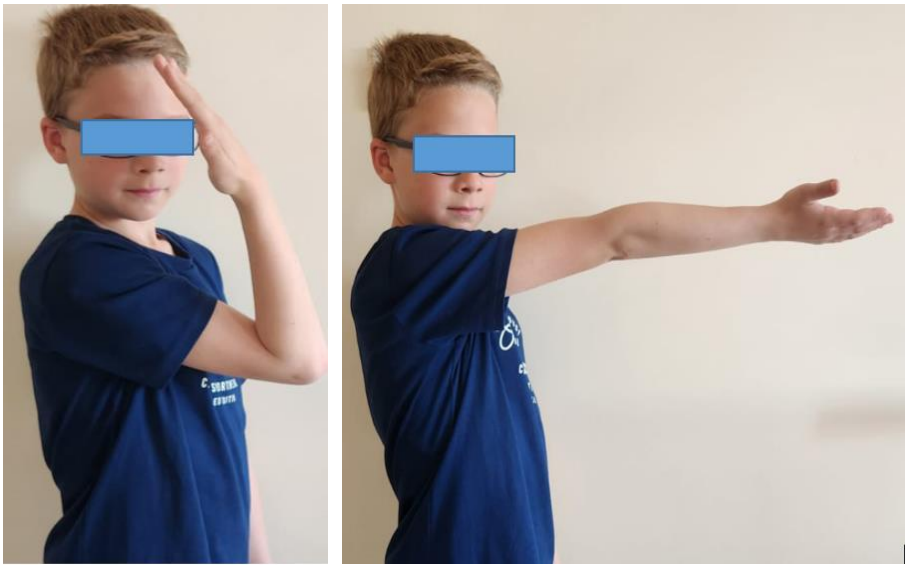


Figure 1.1

Figure 1.2

There is two column at distal humerus. Between that column coronoid and olecranon fossa exist. In the axial plane of that section it looks like dumbbell. When child falls an outstreched arm elbow forces hyperextension (**Figure 1.3**) Olecranon process pressing olecranon fossa and produces extensive force and tenses anterior cortex.(Abraham et al., 1982; Duffy et al., 2021) Extension type supracondylar fractures happens like this. %95 of supracondylar humerus fractures are extension type. But if a child falls on flexed elbow it happens opposite like that. But less common.(Skaggs & Pershad, 1997) (**Figure 1.4**)

Displacement of the distal fragment gives us hints for reduction maneuever. In posteromedial displacement medial periosteum is intact. In posterolateral displacement lateral periosteum is intact. In posteromedial displacement reduction performed in pronation. In posterolateral displacement reduction performed in supination (Smuin et al., 2020).

Figure 1.3 **Figure 1.4**

C) EXAMİNATION

Child must be examinate full body. Any other injuries must be documented. Elbow may be painful, deformed, swollen, bruised, distal of the extremity may be pale.

"Pucker Sign" is indicates the proximal bone fragment may tear brachialis muscle and sticks in to deep epidermis.(Shrader, 2008; Smuin & Hennrikus, 2017) This sign must be alert the clinician about median nerve or brachial artery injury. While performing reduction these structures may be trapped in fracture fragments.(Duffy et al., 2021)

Neurovascular examination must be documented. Neurovascular injuries reported about %49 with high percentage. In the extension type AIN(Anterior Interosseous Nerve) is the most injury and in the flexion type ulnar nerve is the most nerve injury(Babal et al., 2010; Duffy et al., 2021)

Vascular circulation of the distal of the extremity is mandatory. Distal pulses must be palpated. Examination must be performed bilaterally. If neurological deficit and pulseless limb is present surgical emergency should be considered. (Mangat et al., 2009) Performing neurovascular examination is may be very difficult in children. If child scares from surgeon, family could take video and show it to surgeon.

Median nerve should be examinate with saying children to make a fist. Extending fingers for radial nerve. Abducting all fingers for ulnar nerve. Making perfect sign for AIN(Anterior Interosseous Nerve). (Duffy et al., 2021)

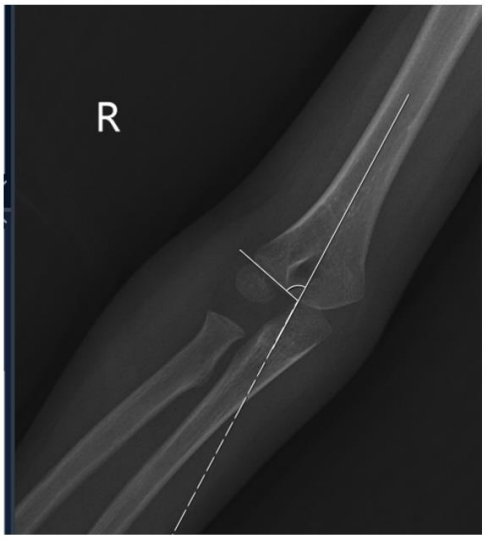
D) RADIOLOGICAL ASSESSMENT

When encountered with elbow trauma anteroposterior and lateral views are mandatory. These radiographs is mandatory for classification, treatment, prognosis.

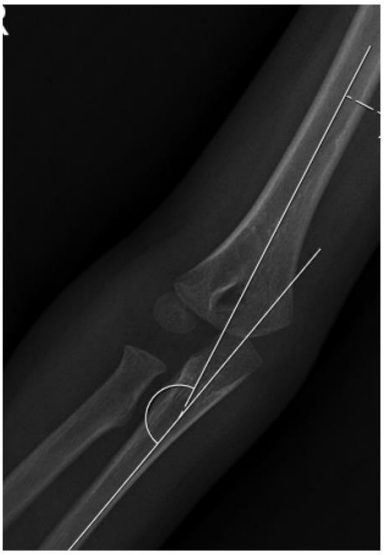
It is not easy assessment of radiological findings in children. Ossification centers changes with age. First ossification center is capitellum and it develops in one year of age(Miyazaki et al., 2017)

In anteroposterior radiographs there is some lines and angles. Baumann's Angle, radiocapitellar line, carry angle are three of them. (Figure 2.1). It is an angle between parallel line capitellar physis and longitudinal axis of the humerus. Normal value of this angle is between 64-81 degrees. If

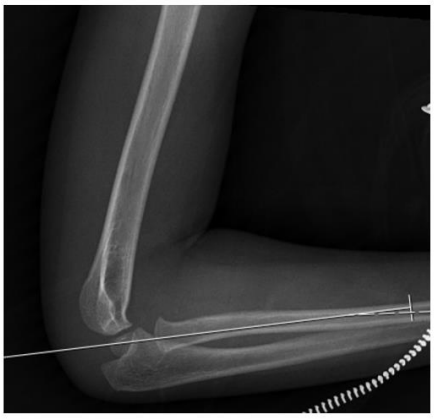
Baumann's angle increased surgeon must be watchful for cubitus varus deformity.(Smajic et al., 2013; Williamson et al., 1992) If we draw a line along the long axis of Radius shaft and this line crosses humeral capitellum this line is radiocapitellar line



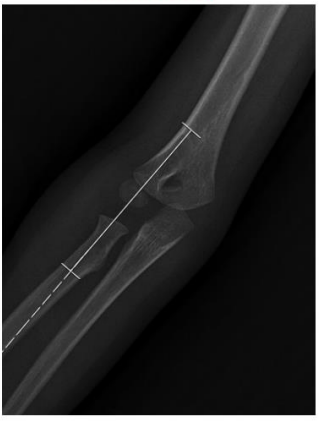
Baumann's Angle



Carrying Angle



Radiocapitellar Line (Lateral)



Radiocapitellar Line (AP)

Figure 2.1

Most of displaced extension type fractures "S-deformity" is present. (**Figure 2.2**)

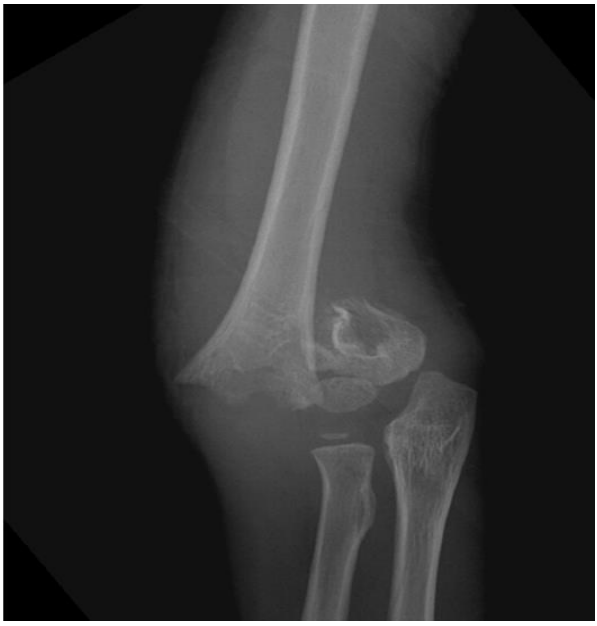


Figure 2.2

Fat Pad sign is the very important sign too. In Supracondylar humerus fractures there is bleeding from bone and this situation causes fat pad elevating from olecranon fossa. With this we can see a radioluscent area on anterior or posterior elbow. Identification of nondisplaced fractures is possible with this sign.(Samelis et al., 2019) (**Figure 2.3**)

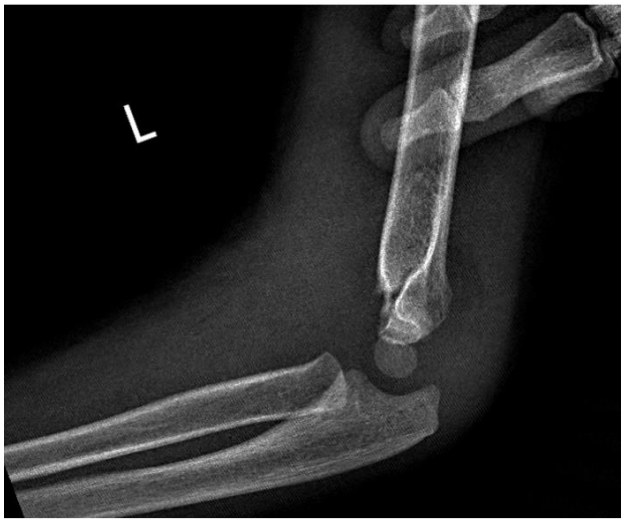


Figure 2.3

Anterior humeral line is the longitudinal line drawn along the anterior humeral cortex on lateral radiograph view must cross the middle third of capitellum. If this line does not cross the capitellum and it is anterior of the capitellum we should think about extension type injury. (**Figure 2.4)**

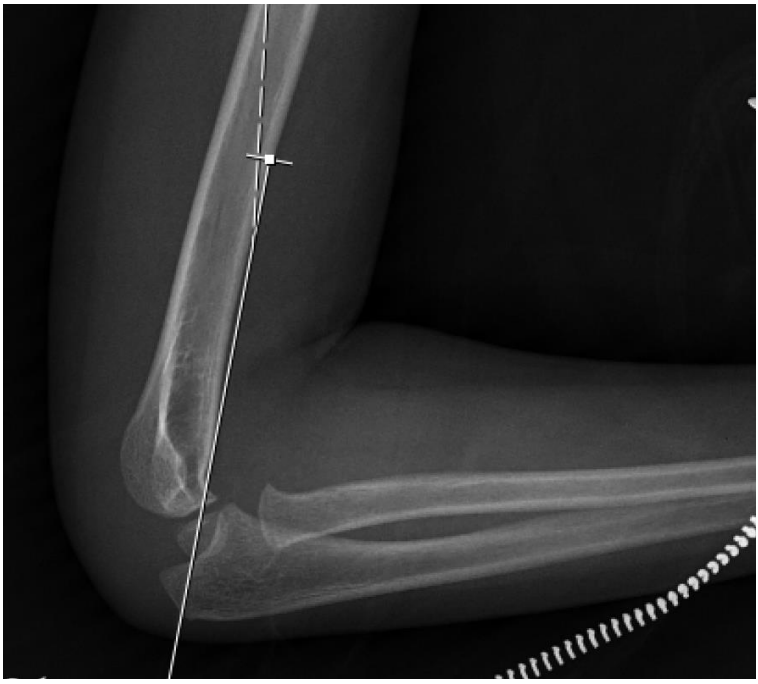


Figure 2.4

E) CLASSIFICATION OF SUPRACONDYLAR HUMERUS FRACTURES

The most supracondylar fracture type is extension type. The most used classfication is Gartland Classification. A lot of classifitions of supracondylar humerus fractures have been suggests. But Gartland's classfication is the most used.(Gartland, 1959) It is based on the portion of displacement of the distal bone fragment.

Type I is non displaced fractures. Anterior Humeral Line crosses the center of capitellum. Periosteum intact and this fractures stable. (**Figure 3.1**)

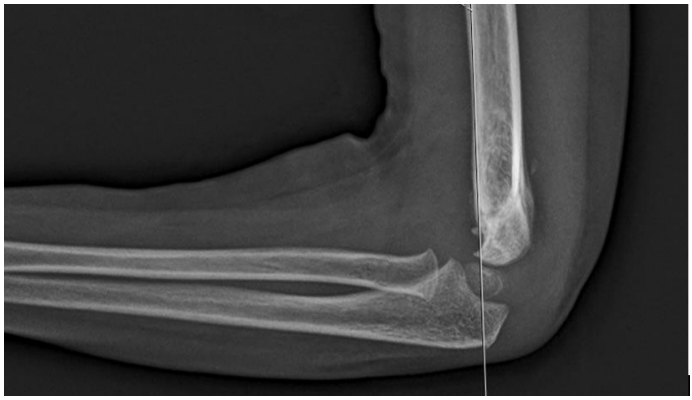


Figure 3.1

Type II is moderately displaced fractures. Anterior Humeral Line passes anterior of the capitellum. Posterior periosteum is intact. It works like hinge. (**Figure 3.2**)

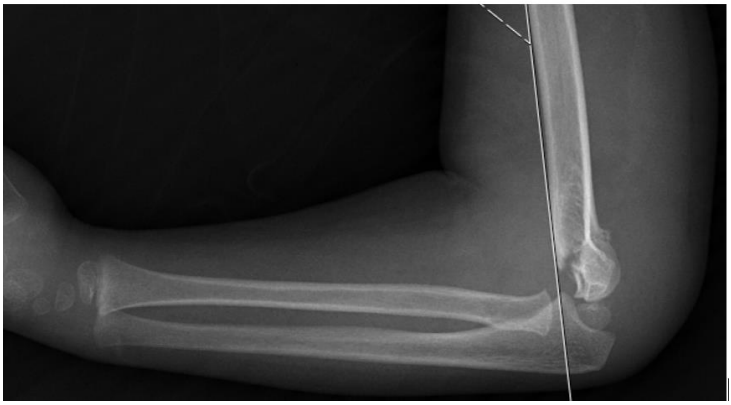
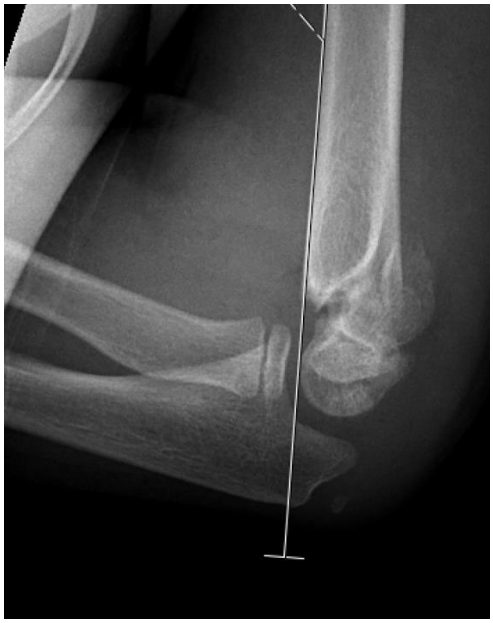


Figure 3.2

Type III is completely displaced. It is unstable, periosteum non intact, soft tissue damage and increased neurovascular structure damage. (**Figure 3.3**)



(**Figure 3.3**)

By Wilkins Gartland's classification modified.Type II fractures divided IIA and IIB according to absence or presence distal fracture fragment malrotation.(Alton et al., 2015) Leitch modified classification too.

Type IV fracture have high instability pattern. This type of fractures only to be recognized intraoperatively.(Leitch et al., 2006)

F) MANAGEMENT AND TREATMENT

1) Non-Operative Management

Non operative management is successful for Gartland Type I or Gartland Type IIA fractures. Type 2A fractures contentious. If medial column comminution is not acceptable varus deformity inevitable.(Labelle et al., 1982)

Contraindications to conservative treatment are posterior displacement, excess swelling, medial comminution. In non operative treatment we are doing above elbow cast that elbow in 80-90 flexion degree. Swelling can pressure on neurovascular structres and lead to compartment syndrome.(Battaglia et al., 2002) At history traction was using for displaced fractures. (Jones, 1977).

2) Surgical Management

Gartland Type II and III fractures are indicated for surgical treatment. Surgical management includes closed reduction-percutaneous pinning with K-Wires or open reduction.(Skaggs et al., 2008) Open reduction indicates for failed closed reduction, vascular injury.

2.A) Closed Reduction-Percutaneous Pin

Gartland Type II and III fractures are indicated for closed reduction percutaneous pinning.

2.B) Closed Reduction

Traction must be performed while elbow is slight flexion. With this alignment will be corrected. Coronal plan deformity will be corrected after traction with doing varus-valgus forces. When pucker sign is present milking maneuver should be performed. This maneuver helps soft tissue releasing.

If posteromedial displacement is present pronation and valgus force should be performed. If posterolateral displacement is present supination and varus force should be performed.

With flexion and extension sagital plane deformities will be corrected. In extension-type fractures hyperflexion should be performed. In flexion-type fractures extension force should be performed.

In multi-directionally unstable fractures joystick technique and external fixator has been described. (Leitch et al., 2006; Novais et al., 2013)

2.C) Percutaneous Pinning

Crossed two pins and lateral pins used mostly. With lateral pins iatrogenic ulnar nerve injury risk is reduced. Lateral pins may be two or three k-wires. It could be performed divergent or parallel but divergent pins has been reported more stable.(Lee et al., 2002) 2mm pins are more stable then 1.6 mm pins.(Gottschalk et al., 2012)

With crossed ping iatrogenic ulnar nerve injury risk is increased. But this construct have more rotational stability from lateral pins.(Babal et al., 2010; Zionts et al., 1994)

For protecting ulnar nerve surgeon should perform medial incision before insterting pin.(Mulpuri & Tritt, 2006) Another way of the protecting

ulnar nerve is medial pin should inserted while elbow extended position. With this maneuver ulnar nerve displaces posteriorly.

2.D) Open Reduction

If closed reduction is not acceptable open reduction indicated. Exploration of neurovascular structures necessary open reduction should considered. Medial,lateral, posterior and anterior approaches should be used.(Ersan et al., 2012; Koudstaal et al., 2002; Vaquero-Picado et al., 2018)

G) MANAGEMENT AND TREATMENT

1) Neurological Injury

Neuropraxia is reported %11.3 incidence. (Babal et al., 2010) Anterior interosseous nerve injury is seen in mostly with extension type supracondylar fracture. Ulnar nerve injury is seen in mostly with flexion type supracondylar fractures. Radial nerve injury is seen in mostly with posteromedial displacement. (Wang et al., 2017)Median nerve injury could be iatrogenic or traumatic.

2) Vascular Injury

Brachial artery compromise is seen with mostly Gartland Type III fractures.(Blakey et al., 2009)

3) Compartment Syndrome

With vascular compromise impaired perfusion occurs with inadequate collateral circulation and this can result compartment syndrome. This situation may leads to limb loss.

4) Volkmann Ischaemic Contracture

With forearm compartment syndrome ischemiae occurs and this situation happens.

5) Malunion-Deformity

Recurvatum deformity is the most seen sagital plane deformity. It is remodelling properly because this deformity is in the plane of elbow movement. Cubitus varus and valgus seen in rotational deformities. Cubitus valgus may be seen with ulnar nerve palsy.

6) Stiffness

Range of motion increases in six weeks after surgery. In 12 months range improves to normal at %98.(Zionts et al., 2009) Stifness has been seen mostly in open reducted fractures.(Vaquero-Picado et al., 2018)

7) Pin Loosening

When changing dressing family and caregiver must be careful. Otherwise pins could migrate.

8) Pin Infection

H) POSTOPERATİVE AND REHABILITATION CARE

Pins usually removed at postoperative 3-4 weeks. When pins are removed range of movement must begin. We can see some stiffness but this situtation is temporary mostly. After first month after surgery range of movement improves rapidly. Young children regain their range of motion fast. In a randomized controlled trial physiotherapy has not been found improve outcomes.(Schmale et al., 2014)

I) INFORMING PATIENT AND FAMILY

Gartland type I and IIA fractures have best outcomes. Children and their caregivers should be informed about severity and prognosis. Despite best treatment sever injuries may result in a late deformity.

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NON-PROSTHETIC TREATMENT OPTIONS FOR JOINT CARTILAGE INJURIES

Erdem ÖZDEN

- Affiliation: University of Health Sciences Gaziosmanpaşa Training and Research Hospital, Istanbul/TURKIYE
- ORCID: 0000-0003-0765-5635
- Mail: ozdenerdem@hotmail.com

INTRODUCTION

Articular cartilage injuries are defined as damages occurring on the joint surface. Such injuries can result from sports activities, traumas, or overuse. Articular cartilage injuries lead to symptoms such as pain, swelling, and limited mobility and can result in osteoarthritis, negatively affecting the quality of life. Nowadays, various options are available for the treatment of articular cartilage injuries. These treatment methods are shaped based on the structure of the joint cartilage, the degree of injury, and associated damages.

Structure of Articular Cartilage

The cartilage covering the surfaces of diarthrodial synovial joints is hyaline cartilage; most collagen in its content is type II collagen (Sophia Fox et al., 2009). Hyaline cartilage is the most abundant cartilage type in the human body (Carballo et al., 2017). Articular cartilage is avascular and does not contain nerve or lymphatic tissue. During the embryological period, chondroblasts derived from mesenchymal stem cells form the cartilage layer, and the basic cell present in the cartilage is chondrocytes, derived from chondroblasts (Sophia Fox et al., 2009). The extracellular matrix is the non-cellular part. This matrix comprises proteoglycans, type II collagen, and predominantly water (Marlovits et al., 2006).

Normal articular cartilage consists of four zones, which are named superficial, middle, deep, and calcified zones, starting from the joint surface. The cell arrangement in each zone is unique (Carballo et al., 2017). In the superficial zone, collagen fibers are parallel to the surface and resistant to shear stress. It is also called the tangential zone due to the arrangement of the fibers. The second zone is the middle or transitional zone. In this zone, shear forces are converted into compressive forces, and the collagen fibers are obliquely oriented. The third zone is the radial zone, where the collagen fibers are now vertically oriented and resistant to compressive forces. The fourth zone is completely calcified and called the calcified zone or "tidemark." It is a barrier between the vascular, well-nourished subchondral bone and the articular cartilage above (Simon & Jackson, 2006).

Due to the structure of articular cartilage, its healing potential varies depending on the degree of injury. The vascularization of injuries that pass through the fourth zone, the calcified area, and those that do not differ leading to different healing potentials. Therefore, when selecting a treatment method,

the lesion's shape, size, depth, and location should be considered. The age and expectations of the patient, load distribution, and joint stability also play an important role in treatment selection (Armiento et al., 2019; Simon & Jackson, 2006).

Treatment Options

Treatment options can be divided into conservative and surgical treatment. In conservative treatment, the aim is to reduce pain and improve the quality of life (Hangody et al., 2018). However, these methods do not result in cartilage repair (Willers et al., 2003).

If the number of cartilage defects in a joint is more than three or if the opposite side of the lesion is also damaged, it is called osteoarthritis (Widuchowski et al., 2007). The literature on conservative treatment methods is generally focused on osteoarthritic joints.

As with any traditional treatment, evidence-based methods should be used when choosing the treatment method for cartilage injuries. The guideline updated in 2021 by the American Academy of Orthopaedic Surgeons (AAOS) can be helpful (Brophy & Fillingham, 2022). The guideline provides recommendations based on strong evidence and presents recommendations with low levels of evidence.

According to this guideline, many high-quality studies demonstrate that exercise and education improve the quality of life in the conservative treatment of weight-bearing joints. Similarly, weight loss significantly improves the quality of life according to this guideline (Messier et al., 2013; Mihalko et al., 2019).

Regarding pharmacological treatments, we can initially continue conservative treatment with paracetamol, followed by non-steroidal anti-inflammatory drugs (NSAIDs) that are oral or topical and non-steroidal. However, routine use of opioids is not recommended. It should also be noted that oral medication can have gastrointestinal (GI) and cardiovascular system (CVS) side effects. Evidence for the benefits of oral supportive therapies such as curcumin (Turmeric extract), ginger, glucosamine, chondroitin, and vitamin D is also low (Brophy & Fillingham, 2022; Feng & Beiping, 2017; Hammad et al., 2015; Haroyan et al., 2018).

There is sufficient evidence in the literature demonstrating the beneficial effects of intra-articular steroid injections, although their effects last

about three months. The situation is different for hyaluronic acid injections. The previous AAOS (American Academy of Orthopaedic Surgeons) guideline published in 2013 emphasized that hyaluronic acid injections are inappropriate. However, in the latest guideline, evidence supporting this negative view has been lowered, indicating that hyaluronic acid injections can be considered in appropriately selected patients, and it is important to keep up with new developments (Brophy & Fillingham, 2022; Hangody et al., 2018; Petrella & Petrella, 2006; Raynauld et al., 2003). The level of evidence for platelet-rich plasma treatments is limited (Brophy & Fillingham, 2022; Simental-Mendía et al., 2016; Spaková et al., 2012; Zhang, 2018). In addition, there are many conservative treatment methods, such as transcutaneous electrical stimulation, manual therapy, massage, and laser therapy. However, they have not reached a high level of evidence regarding their benefits (Brophy & Fillingham, 2022; Cherian et al., 2016; Hungerford et al., 2013; Palmer et al., 2014).

In surgical treatment, the goal is generally to achieve biological repair for local cartilage injuries before they progress into degenerative joint disease, or if they cannot be repaired, to improve quality of life through palliative or reconstructive (non-biological) methods. Reparative and restorative treatments are called biological repair (Figure 1).

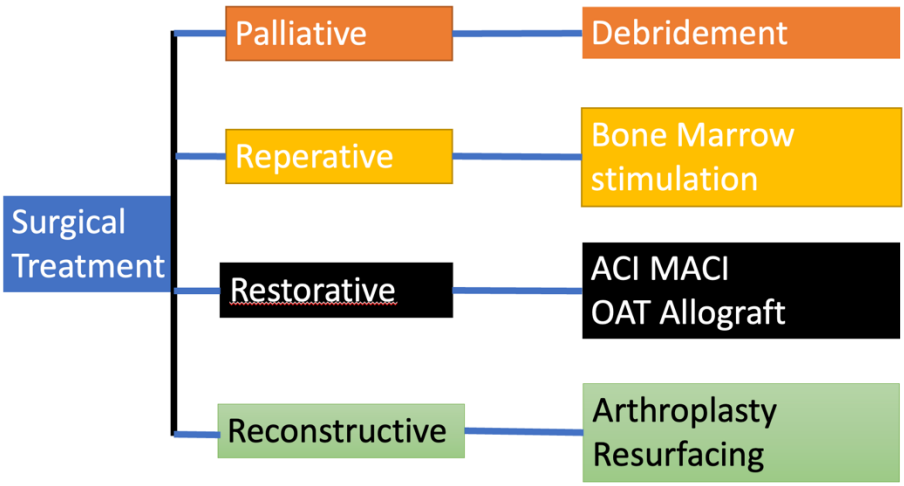

Figure 1 - Surgical treatment options diagram

ACI: autologous chondrocyte implantation, MACI: matrix-assisted autologous chondrocyte implantation, OAT: osteochondral autograft transfer.

1-Palliative Treatment

One of the first options that come to mind is irrigation and debridement, aiming to clean intra-articular loose particles and mediators. However, a prerequisite for palliative and biological treatments is the absence of advanced degeneration, inflammatory arthritis, proper and stable alignment, body mass index not exceeding 25, and absence of corresponding (kissing) lesions. Irrigation and debridement are suitable for defects smaller than 1 cm (Brophy & Fillingham, 2022; Heybeli et al., 2008; Saeed et al., 2015; Vad et al., 2003).

2- Reparative Treatment

The reparative treatment bridges avascular cartilage tissue and subchondral bone and promotes hemorrhage. There are different methods available for this stimulation.

Open abrasion technique was described by Magnuson where the subchondral area can be reached using a shaver. It was first applied arthroscopically by Johnson in the 1970s, and a success rate of 66% was reported at the 1982 AAOS Congress (Lee et al., 2022; MAGNUSON, 1946). However, Dr. Clement stated that the results of the technique were not good and that only Dr. Johnson could achieve this success, leading to a loss of popularity of the technique despite Dr. Johnson's subsequent publications (Johnson, 1986). In 2015, it was reported to provide good results in patients under 50 with medial femoral condyle defects smaller than four centimeters in osteoarthritic knees. However, it is not a commonly used technique (Lee et al., 2022; Lubowitz, 2015; Sansone et al., 2015). Yamada et al. reported good results in 11 out of 18 patients with degenerative conditions of the medial femoral trochlear cartilage detected during arthroscopic examination after high tibial osteotomy using abrasion arthroplasty (Yamada et al., 2021).

The microfracture technique, popularized by Steadman and colleagues, remains a commonly used method. In this technique, after the damaged cartilage is debrided using a curette, small holes with a depth of 2 mm and a diameter of 2.5 mm are created from the periphery to the center using an angled awl-like instrument. A 3 mm gap is left between the holes to allow the migration of mesenchymal stem cells (Insall, 1974; Madry et al., 2017; Pridie, 1959; Steadman et al., 1999).

To create microfractures, an angled and backward-widening awl is used. However, it has been suggested that during this process,

microarchitecture in the subchondral area may be disrupted, and the channels can become narrow and blocked, leading to the formation of cysts (H. Chen et al., 2009). As an alternative, the nano-fracture technique has been developed. In this technique, using a 1 mm diameter Nitinol needle within a 15-degree angled cannula, holes are created at depths of 6-9 mm (Warren et al., 2022; Zedde et al., 2017). Zedde et al. reported in 2016 that the nano-fracture technique was superior to microfracture as it could reach deeper regions without compressing the subchondral area during the procedure (Zedde et al., 2016).

A recent animal experiment study published in 2022 reported that subchondral drilling provides better cartilage repair compared to debridement alone (Stachel et al., 2022). Demange et al. demonstrated that after microfracture was performed with an awl, there was a high probability of osteophyte formation within the lesion, similar to the healing response seen in fractures (Demange et al., 2017). Subsequently, these patients underwent ablation and autologous chondrocyte implantation (ACI), and minimal reoccurrence of osteophyte formation was reported.

In reparative treatments, healing is achieved with fibrocartilage containing Type 1 collagen instead of the original hyaline cartilage containing Type 2 collagen, which is a less durable structure (Simon & Jackson, 2006). Restorative treatment methods have been developed to enhance hyaline cartilage formation. These include autologous chondrocyte implantation (ACI), matrix-assisted autologous chondrocyte implantation (MACI), osteochondral autograft transfer (OAT), and allograft applications.3-

Restorative treatments

Restorative treatments aim to restore hyaline cartilage, the joints' original and highly durable form of cartilage. Several techniques have been developed for restorative treatment:

Autologous Chondrocyte Implantation (ACI):

Autologous chondrocyte implantation is a two-stage surgical technique (Seo et al., 2011). In the first stage, a biopsy is taken from a non-weight-bearing area of healthy cartilage, and the obtained chondrocytes are multiplied in the laboratory. During the biopsy, it is necessary to obtain approximately 200 to 300 mg of cartilage (L Carey et al., 2021). The harvested cells can be cryopreserved and stored for up to five years. The 15-20 million cells required

for implantation can be produced within 3-4 weeks using autologous serum and growth factors. In the second stage, after debridement of the damaged area, a periosteal graft taken from the tibia is typically used to cover the area. The graft is protected with a fibrin adhesive to create a sealed environment, and chondrocytes are injected into it. Therefore, the cambium cells from the periosteum are also utilized. It has been reported that the implanted chondrocytes can activate periosteal chondrogenesis by producing TGF-B. However, complications such as periosteal delamination, periosteal hypertrophy, uneven distribution of cells, or leakage from the periosteum can occur (Marlovits et al., 2006; Seo et al., 2011; Simon & Jackson, 2006).

Second-generation ACI uses a biological membrane instead of a periosteum to prevent periosteal thickening. The surgical technique remains the same. Since periosteum is not harvested, it requires fewer incisions and has a higher cost. Complications such as uneven distribution of cells and leakage can still occur (Marlovits et al., 2006).

Matrix-induced Autologous Chondrocyte Implantation (MACI):

In the third generation, these chondrocytes are produced directly on a collagen matrix, with a density of 500,000 to 1 million cells per square centimeter. The matrix is then cut to match the size of the defect and applied. It adheres without the need for sutures using a fibrin adhesive. This technique is MACI or ACI-collagen (Marlovits et al., 2006).

In this technique, attention should be paid to the content of the applied cartilage scaffold. As stated on the original website "www.maci.com," it is contraindicated in individuals with allergies to aminoglycosides, bovine or porcine products. Various forms of scaffolds or cartilage matrices have been developed. They can be made of proteins (such as fibrin, collagen, gelatin, etc.), carbohydrates (such as hyaluronan, agarose, alginate, polylactic acid, polyglycolic acid, etc.), synthetic polymer-based materials (such as hydroxyapatite, polyethylene glycol, etc.), or combinations thereof. The most commonly used ones are collagen, hyaluronan, and hybrid scaffolds.

Regarding recent advancements, studies on applying these cartilage scaffolds in combination with microfracture techniques without cells show promising results (Andriolo et al., 2021; G. Chen et al., 2016; Kwan et al., 2020). However, currently, they are primarily recommended for small defects.

Osteochondral Autograft Transfer System (OATS):

In ACI and MACI, chondrocytes are implanted, while in full-thickness defects, the OATS can be used. Since it is osteochondral, the chondrocytes on the surface are transferred along with the underlying live bone without detachment (Rowland et al., 2019). Grafts are typically taken from the non-weight-bearing superolateral aspect of the femur. It is suitable for individuals between 15 and 50 who have completed skeletal maturation but are not yet ready for joint replacement. The lesion should be focal and full-thickness, and the corresponding area of the joint should be intact. The body mass index should not exceed 35. Minimal or no joint degeneration should be present, the surrounding hyaline cartilage should be intact, and the joint should be stable with proper alignment (Baltzer et al., 2016; Emre et al., 2013; Rowland et al., 2019).

OATS may not be suitable for large defects due to donor site morbidity. It is typically performed through a mini-arthrotomy. The size of the donor site limits the size of the area to be treated. One advantage is that it is a single-stage surgery, but achieving a press-fit placement can be challenging, and three months without weight-bearing is required (Rowland et al., 2019).

In cases where autografts, such as OATS, may be insufficient, allografts come into play. This procedure is called osteochondral allograft transplantation. Advantages of using allografts include the avascular and aneural nature of articular cartilage, the ability to store grafts easily, and the absence of immune-triggering properties. However, up to 67% sensitization rates have been reported following allograft transplantation (Stone et al., 2018; Strong et al., 1996). Allografts can be transferred after necessary testing for aerobic, anaerobic, spore-forming bacteria, viral infections, and serology, typically taking at least two weeks (McAllister et al., 2007; Torrie et al., 2015).

In order to increase the success rate of these techniques, the use of bone marrow aspirate concentrate has been introduced. Bone marrow aspirate is obtained from suitable areas and then centrifuged to obtain a concentrated form. This technique, as reported by Gao et al., has shown good clinical results in a two-year follow-up study with 20 patients, with graft integration of 80% and defect filling of 70% observed in magnetic resonance imaging (Madry et al., 2017).

In another study, it has been reported that bone marrow stimulation is achieved through nano-fracture, and then it is covered with a cell-free scaffold, resembling a kind of one-stage MACI procedure (Peñalver et al., 2020). It has been reported that this technique has advantages over the standard MACI technique, such as being a one-stage procedure, facilitating the settlement of chondrocytes into the matrix through nano-fracture, and promoting vascularization of the cartilage surface.

With technological advancements, three-dimensional bio-printers have been used to simulate scaffolds (Lafuente-Merchan et al., 2022). Autologous hyaline-like cartilage tissue has been produced and utilized through tissue engineering using cells obtained from nasal chondrocytes under local anesthesia (Mumme et al., 2016). In the study by Chen et al., it was demonstrated in an animal experiment that the chondrogenic properties of nasal chondrocytes are enhanced when produced in a three-dimensional alginate culture rather than a monolayer environment (W. Chen et al., 2018). In this experimental study, injectable alginate hydrogel was applied to the defects, and histological examinations were performed at 3 and 6 months, yielding results close to normal hyaline cartilage.

CONCLUSION

One should know all the methods used to treat cartilage defects and determine the treatment approach based on factors such as the patient's physiological condition, as well as the size and location of the lesion. Technological advancements hold promising prospects for the future utilization of non-prosthetic treatment options. New studies showed the potential for improving the success rates of cartilage restoration techniques and the development of innovative approaches in tissue engineering and regenerative medicine. However, further research and clinical studies are necessary to validate and optimize these methods for widespread clinical use.

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PERSONALIZED MEDICAL GRAFT AND GRAFT MOLDING SUPPORTED BY ARTIFİCIAL INTELLIGENCE

Başak ÇAKMAK

- Affiliation: Istanbul Technical University, Istanbul/TURKIYE
- ORCID: 0000-0002-0116-8863
- Mail: cakmak22@itu.edu.tr

Giray ÖTKEN

- ORCID: 0009-0004-4130-1384
- Mail: girayotken@gmail.com

Ahmet Tolgay AKINCI

- Affiliation: Trakya University, Faculty of Medicine Department of Neurosurgery, Edirne/TURKIYE
- ORCID: 0000-0002-9937-076X
- Mail: ahmettolgayakinci@gmail.com

INTRODUCTION

The advent of technology has revolutionized various sectors, including healthcare, where it has played a significant role in improving patient outcomes. This chapter delves into the intersection of technology and healthcare, focusing on the development of personalized medical grafts and graft molding systems supported by Artificial Intelligence (AI). A novel understanding is introduced, which leverages AI to enhance the process of cranioplasty, a surgical procedure that involves the repair of defects or deformities in the skull (Edelmers et al., 2022). The chapter begins by exploring the use of customized grafts in cranioplasty, detailing the process of creating these grafts using computer-aided design (CAD) software and 3D imaging techniques (Kung et al., 2020). Despite the significant strides made in this field, challenges persist, including the time-consuming nature of the design process and complications associated with graft materials (Tantisatirapong et al., 2023). To address these challenges, the use of Generative Adversarial Networks (GANs) is introduced in the creation of 3D models for medical imaging and 3D printing (Goodfellow et al., 2014). GANs have been employed in the generation of high-quality, realistic 3D models from various types of input data, proving particularly useful in medical imaging where patient-specific models are required (Hong et al., 2021; Guha et al., 2020). The chapter further discusses the efficacy and usefulness of AI-assisted design and modeling in the production of grafts and graft molds using 3D printing technology. This process involves the analysis of 3D tomography data, AI-assisted design and modeling, and the production of grafts and graft molds using 3D printing technology. The integration of these fields aims to address the needs of patients in a novel way, providing significant advantages in terms of time, precision, and cost. The chapter concludes by detailing the methods involved in using a series of techniques to detect and reconstruct damaged or missing bone parts in 3D. The methods are divided into two main components: image processing and object detection using a Convolutional Neural Network (CNN) model, followed by 3D reconstruction and correction of damaged or missing bone parts using a Generative Adversarial Network (GAN) model (Chang et al., 2021). A comprehensive overview of the advancements in the field of cranioplasty is provided, highlighting the potential of AI in improving patient outcomes. It serves as a valuable resource for medical practitioners, researchers, and anyone interested in the intersection of healthcare and technology.

CUSTOMIZED GRAFTS IN CRANIOPLASTY

Cranioplasty is a surgical procedure that involves the repair of defects or deformities in the skull. One of the most common reasons for cranioplasty is to replace missing parts of the skull, often resulting from trauma, tumor resection, or congenital defects (Edelmers et al., 2022). The completion of these missing parts is typically achieved through the use of customized grafts, which are designed to match the patient's unique anatomy and restore the skull's original shape and function (Li et al., 2021). The process of creating these customized grafts involves several steps. First, a detailed image of the patient's skull is obtained, typically through computed tomography (CT) scans (Zheng et al., 2009). These scans provide a three-dimensional (3D) representation of the skull, which can be used to identify the size, shape, and location of the missing part. Next, this 3D image is used to design a graft that perfectly fits the defect. This design process often involves the use of computer-aided design (CAD) software, which allows for precise control over the graft's shape and size (Kung et al., 2020). Once the graft design is complete, it is fabricated using various materials. These materials can include autografts (bone taken from another part of the patient's body), allografts (bone taken from a donor), xenografts (bone taken from a different species), or synthetic materials such as polymethylmethacrylate (PMMA) or hydroxyapatite (Li et al., 2021). The choice of material depends on several factors, including the size and location of the defect, the patient's overall health, and the surgeon's preference (Kashyap et al., 2018). The use of CAD and 3D imaging in the design and fabrication of customized grafts has significantly improved the outcomes of cranioplasty procedures (Kung et al., 2020). These technologies allow for a high degree of precision in graft design, resulting in a better fit and more natural appearance. Furthermore, they can reduce the time and cost of surgery by allowing for preoperative planning and the fabrication of the graft before the actual surgery (Pimentel et al., 2020).

In this section, 3D models of the missing cranial bones for three patients in need of cranioplasty created based on tomographic data are shown. These models were edited using 3D modeling software. The necessary 3D graft models and their corresponding negative graft molds were created using classical polygonal modeling and Boolean operations, ensuring accurate measurements. These models were then converted to the STL file format, ready for 3D printing. Subsequently, negative molds were designed for the anatomically accurate graft models using the same software, and these molds

were 3D printed using PLA material and sterilized before surgery. The produced grafts were utilized in three surgeries (Figure 1).

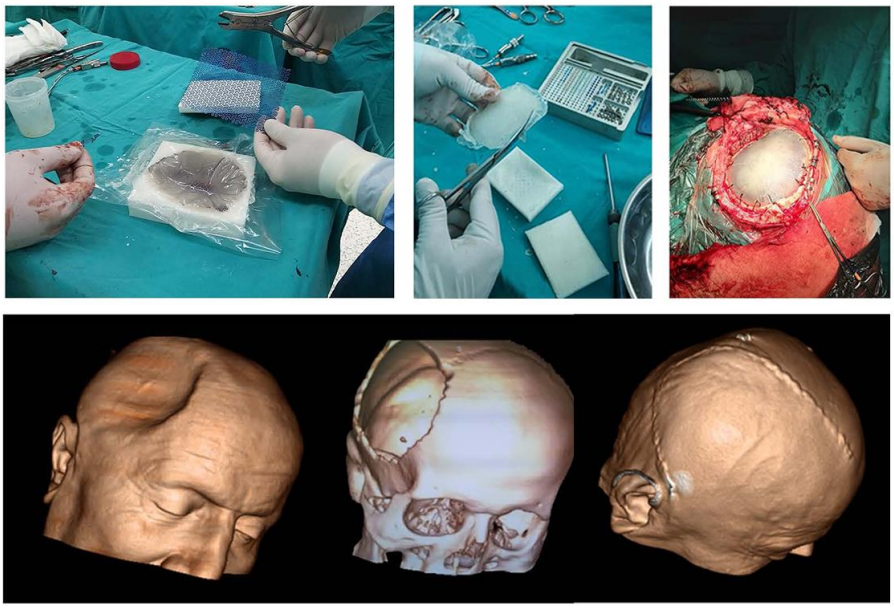

Figure 1. Graft mold produced with CAD and its clinical application

However, despite these advances, there are still challenges associated with the use of customized grafts in cranioplasty with CAD. For example, the process of designing and fabricating the graft can be time-consuming and requires specialized equipment and expertise (Tantisatirapong et al., 2023). Additionally, there can be complications associated with the graft material, such as infection, rejection, or resorption (Li et al., 2021). Future research in this area would focus on improving the design and fabrication process, developing new and better materials for grafts, and finding ways to reduce complications (Tantisatirapong et al., 2023). The completion of missing skull parts with customized grafts is a critical aspect of cranioplasty. The use of CAD and 3D imaging has greatly improved the process, but there are still challenges to be addressed. As technology continues to advance, it is likely that the outcomes of these procedures continue to improve (Kung et al., 2020). In this direction, the chapter explains the methods for the use of Artificial Intelligence (AI) supported systems in cranioplasty applications.

GENERATIVE ADVERSARIAL NETWORKS

Generative Adversarial Networks (GANs) have emerged as a powerful tool for generating 3D models, particularly in the field of medical imaging and

3D printing. GANs are a type of machine learning model that consists of two neural networks, a generator and a discriminator, which are trained simultaneously. The generator creates new data instances, while the discriminator evaluates them for authenticity; i.e., whether they belong to the actual training dataset or were created by the generator. The goal is to improve the generator's ability to create realistic data and the discriminator's ability to distinguish real data from generated ones (Goodfellow et al., 2014). In the context of 3D model generation and printing, GANs have been used to create high-quality, realistic 3D models from various types of input data. For instance, Hong et al. (2021) developed a 3D-StyleGAN, a style-based GAN for the generative modeling of three-dimensional medical images. This model was able to generate high-quality 3D models that could be used for various medical applications, including surgical planning and patient-specific implant design.

Similarly, Guha et al. (2020) used GANs for high-resolution reconstruction of trabecular bone microstructures from low-resolution CT scans. Their model, GAN-CIRCLE, was able to generate high-quality 3D models of bone structures, which could be used for various biomedical applications, including the design and fabrication of patient-specific implants. In addition to medical imaging, GANs have also been used for 3D model generation in the field of design and manufacturing. For example, Çakmak and Öngün (2023) used deep generative models to represent design cognition in 3D modeling. Their model was able to generate complex 3D designs that could be used for various applications, including 3D printing. GANs offer a powerful tool for generating high-quality, realistic 3D models from various types of input data. Their ability to generate complex 3D structures makes them particularly useful in fields such as medical imaging and 3D printing, where high-quality, patient-specific models are required.

EFFICACY AND USEFULNESS

The chapter explains the production of customized graft molds for patients with deficiencies in the skull region via artificial intelligence. This process involves the analysis of 3D tomography data, AI-assisted design and modeling, and the production of grafts and graft molds using 3D printing technology. The efficacy of the process extends to several areas:

- **3D Tomography Data Analysis:** The process involves the analysis of 3D tomography data to identify the specific needs of each patient. This

allows for the creation of grafts that are perfectly tailored to each patient's anatomy, reducing surgery time and the risk of complications.

- **AI-Assisted Design and Modeling:** The process leverages artificial intelligence and machine learning technologies to assist in the design and modeling of grafts. This increases the speed and accuracy of the graft production process.
- **3D Printing of Grafts and Graft Molds:** The process utilizes 3D printing technology to produce the grafts and graft molds. This allows for the rapid production of customized grafts, further reducing surgery time and improving patient outcomes.
- **Integration of Different Disciplines**: The process aims to integrate the fields of medicine and information technology to address the needs of patients in a novel way. This includes addressing operational needs that are not routinely encountered, 3D modeling processes that require anatomical knowledge and accuracy, the need for meticulous personalized production, and the lack of expert personnel to implement these.

The significant aspect of this chapter lies in the combination of machine learning and artificial intelligence technologies with anatomical 3D modeling and 3D printing. This combination makes the process of customized graft production faster, more accurate, and more economical. Furthermore, the use of a Generative Adversarial Network (GAN) trained 3D modeling and customized software allows individuals who are not proficient in complex graphic programs to manage this process, providing significant advantages in terms of time, precision, and cost. GAN algorithms and 3D printing technology are already being successfully used by researchers worldwide. The combination of these technologies, especially in medical research, offers great potential.

METHODS

The methods explained in the section involve using a series of techniques to detect and reconstruct damaged or missing bone parts in 3D. The methods are divided into two main components: image processing and object detection using a Convolutional Neural Network (CNN) model, followed by 3D reconstruction and correction of damaged or missing bone parts using a Generative Adversarial Network (GAN) model. The Mask R-CNN model is used to detect damaged or missing bone parts, while the 3D-

GAN model is used for reconstruction and correction. The 3D-GAN model includes a generator and a discriminator working together to progressively create more realistic bone structures. The output of the generator, planned to be designed in the PyTorch Framework, is used for 3D bone reconstruction (Chang et al., 2021). The workflow diagram for the proposed methods is illustrated in Figure 2. Each part is integral to the process and has been carefully designed to ensure the validity and reliability of the expected outcomes.

Training data is acquired via the Picture Archiving and Communication Systems (PACS) service provided by Sectra. PACS is a system utilized for the storage, access, and management of medical imaging data (Inamura & Jong, 2011). The training data is obtained in the Digital Imaging and Communications in Medicine (DICOM) format. DICOM is a standard for the storage and transmission of medical imaging information, typically used in radiology, cardiology, and other medical imaging disciplines (Pianykh, 2008). This process is of critical importance for success, as the training data is necessary for the system to operate accurately and effectively. This data is used during the development and testing phases of the system, thereby assisting us in evaluating the performance and accuracy.

Detection of Damaged or Missing Bone Parts

The process of detecting damaged or missing bone fragments involves the use of Mask R-CNN (He et al., 2017). This process primarily includes the analysis of 3D images to identify bone fragments that are damaged or missing. This analysis leverages the ability of Mask R-CNN to recognize complex structures and objects (He et al., 2017). Mask R-CNN employs a bounding box predictor and a mask predictor to determine the class and bounding box of each object in an image (He et al., 2017). This is crucial in identifying damaged or missing bone fragments as these parts often exhibit a different appearance from the normal bone structure, and these differences can be detected by Mask R-CNN (He et al., 2017). An approach proposed by Liu et al. (2018) aims to enhance the accuracy and efficiency of bone and cartilage segmentation by combining deep learning and 3D deformation modeling. This approach utilizes SegNet, a CNN technology, and 3D deformation modeling maintains the overall shape by preserving the output of SegNet, providing a smooth surface desirable for musculoskeletal structure (Liu et al., 2018). This method is useful for performing bone and cartilage segmentation swiftly and accurately and holds promising potential applications in musculoskeletal

imaging (Liu et al., 2018). This plays a significant role in detecting damaged or missing bone fragments, as these parts often exhibit a different appearance from the normal bone structure, and these differences can be detected with such a deep learning and 3D deformation modeling approach (Liu et al., 2018).

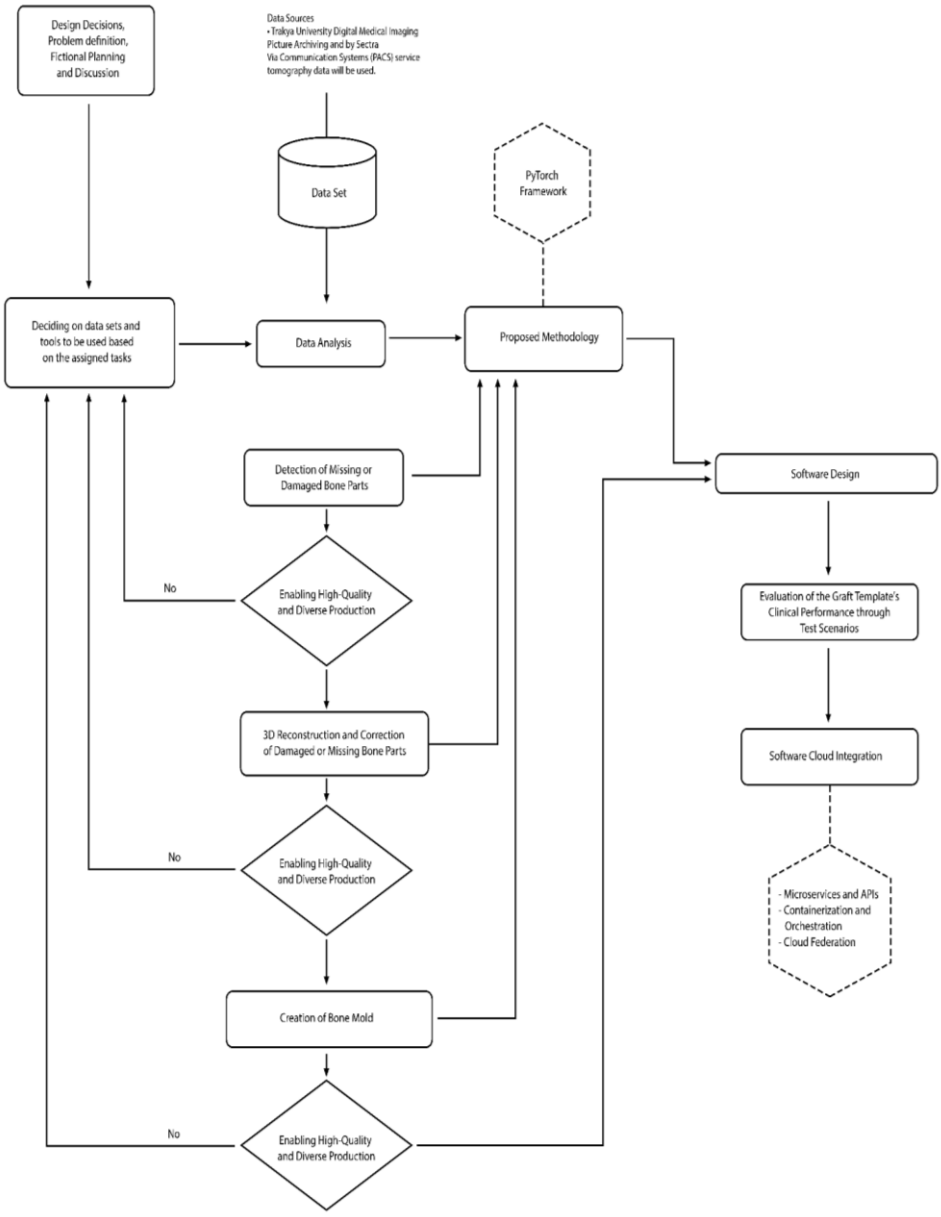

Figure 2. Workflow Diagram

3D Reconstruction and Correction of Damaged or Missing Bone Parts

The process of 3D reconstruction and correction of damaged or missing bone parts involves several steps, including preprocessing, training of Mask R-CNN, training of 3D-GAN, and production of corrected 3D bone models (Figure 3). As indicated in the study titled "Generation of Synthetic CTs from Magnetic Resonance Images" by Emami et al. (2018), the 3D reconstruction and corrections of damaged or missing bone fragments can be enhanced using Generative Adversarial Networks (GANs). GANs are a type of deep learning model that trains two competitive networks simultaneously. In the context of medical imaging, one network, referred to as the generator, is used to generate data (in this case, synthetic CT images), while the other network, referred to as the discriminator, is used to distinguish between synthetic and real data. The study conducted by Emami et al. (2018) demonstrated that GANs can effectively and accurately generate synthetic CT images from T1-weighted MRI inputs within seconds, outperforming traditional deep convolutional neural networks (CNNs). This method offers strong potential to support real-time MR-guided treatment planning in the brain, which can be extended in the context of reconstruction and corrections of damaged or missing bone fragments.

The GAN model uses a residual network (ResNet) as the generator and a CNN as the discriminator. The ResNet generator architecture has shortcut connections for each ResNet block that skips one or more layers. These shortcut connections are identity mappings used to add the input of each block to its output. These methods facilitate the training of the deep network without adding extra parameters or computational complexity. The discriminator network of the GAN model is a CNN with five convolutional layers followed by batch normalization and ReLU, which classify whether an input image is real or synthetic. The discriminator can assist the generator network in producing more realistic synthetic CT output from the MRI input.

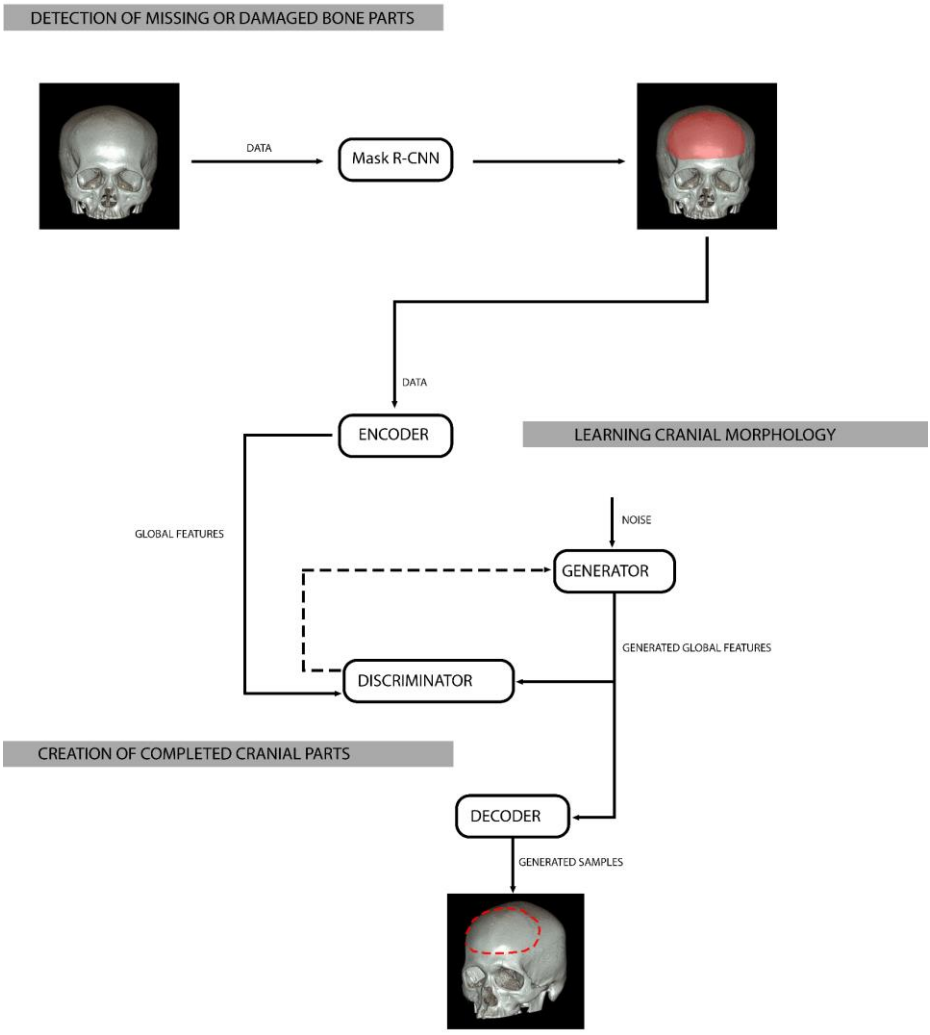

Figure 3. Methodology Diagram

Preprocessing

This process involves the cleaning, normalization, and conversion of the data into an appropriate format. Initially, data obtained from CT scans are converted from the DICOM format to the NIfTI format. This is a more suitable format for the subsequent processing of the data (Tantisatirapong et al., 2023). Subsequently, each image in the dataset undergoes a series of operations to separate bone tissue from other tissues. This is typically accomplished by setting a threshold value and zeroing all pixels below this threshold. This process reduces noise in the dataset and enables the model to more accurately

recognize bone tissue (Kung et al., 2020). Finally, the dataset is normalized to facilitate faster and more effective learning during the model's training. This is usually done by subtracting the mean of the data and dividing by the standard deviation. This process transforms the distribution of the data into a standard normal distribution, which makes it easier for the model to process the data (Kung et al., 2020). These preprocessing steps enable the model to process the data more effectively and produce more accurate results. Additionally, this process reduces the model's training time and enhances its overall performance.

Training of Mask R-CNN

The training of Mask R-CNN is conducted using a convolutional neural network (CNN), which is a deep learning-based change detection framework. This framework is designed to identify varying instances and pixels from very high-resolution (VHR) images (Ji et al., 2019). A notable advantage of this framework is its self-training capability, which is of paramount importance in deep learning-based change detection applications, as high-quality and numerous change examples cannot always be readily provided for training a successful deep learning model.

The framework consists of two parts: a subtraction network and a change detection network. The subtraction network is implemented using a Mask R-CNN for object-based instance segmentation and a multi-scale fully convolutional network for pixel-based semantic segmentation. The change detection network takes the two temporal maps generated from the subtraction network as input and extracts a change map at both object and pixel levels. The change detection network is well-trained without real-life examples by simulating random changes and various parallaxes in its binary map. This significantly reduces the requirements for labeled changes and guarantees the algorithm's resilience to registration errors caused by parallax. This approach can be utilized in the training process of Mask R-CNN for detecting damaged or missing bone fragments, which is a crucial step for bone modeling. This ensures the accurate segmentation of bones for subsequent use in 3D reconstruction.

Training of 3D-GAN

The 3D-GAN is a type of Generative Adversarial Network (GAN) used in the generation of 3D objects. This network comprises two networks competing against each other to produce an output object: a generator and a

discriminator. While the generator network attempts to create realistic-looking fake inputs, the discriminator network strives to classify real and fake inputs. Such competitive training enhances the generalization ability of the discriminator network, which is crucial in situations where training examples are limited. The training of the 3D-GAN is used for the 3D reconstruction of damaged or missing bone fragments. Specifically, the 3D-GAN is employed to complete missing bone parts. This is vital for creating a realistic and accurate 3D bone model. The training of the 3D-GAN consists of a series of steps. Initially, the network is trained with real bone data. This data is obtained from 3D scans of real bones. Subsequently, the network is used to complete missing bone parts. This is done using the information the network has learned to complete the missing parts. Finally, the network is tested to verify that the generated 3D bone model is realistic and accurate (Zhu et al., 2018). This technique is an effective method for the 3D reconstruction of damaged or missing bone fragments. The 3D bone model generated and corrected by the 3D-GAN is made ready for use in real-world applications. This process outlines and tests the steps for the design and production of a specific medical graft or graft mold from the patient's CT data.

Performance Evaluation

Performance evaluation is a critical step in measuring the effectiveness of models such as Mask R-CNN and 3D-GAN. It is intended that these methods enable the creation of a model that can automatically perform the 3D reconstruction of a specific patient's damaged or missing bone fragments. However, these methods require a large amount of labeled data to function correctly (Wu et al., 2016). Furthermore, validation on a broad and diverse test set is necessary for the model to be applicable in the real world (Pedoia et al., 2019). The next stage is to determine how effective these methods are for clinical applications. This involves evaluating how well the model generalizes to different types of bone damage and various demographic characteristics of patients (Pedoia et al., 2019). For Mask R-CNN, a metric such as Intersection over Union (IoU) is typically used (He et al., 2017). This metric is widely used in object detection and instance problems and calculates the ratio of the intersection to the union between the predicted and actual bounding boxes (Girshick et al., 2014). On the other hand, for 3D-GAN, a metric like Fréchet Inception Distance (FID) could be ideal (Heusel et al., 2017). FID measures the statistical difference between real and generated images, with lower values indicating better model performance (Lucic et al., 2018). Finally, these methods may require further research, particularly regarding the performance

of the 3D-GAN on real-world data. Current 3D-GAN models are typically trained with idealized data, but real-world data is often more complex and irregular. Therefore, further research into how such models can handle real-world data would be beneficial (Wu et al., 2016).

Production of Graft Mold

Following the construction of the corrected 3D bone model, it is necessary to create a graft mold to utilize this model in clinical applications. This process involves a series of programming and mathematical operations, and a variety of software libraries and algorithms are employed to facilitate its implementation. The process of creating the graft mold begins with the selection of an initial 3D volume and the extraction of the corrected 3D bone model from this volume. This process is executed through an operation known as a Boolean subtraction (Botsch et al., 2006). The Boolean subtraction operation enables the calculation of interactions between geometric bodies. In situations where two or more 3D models are combined, the Boolean subtraction operation identifies areas where one model intersects with another. In this process, a subtraction operation is performed using a predetermined 3D volume (typically a cube or cylinder) and the corrected 3D bone model. A second 3D model (in this case, the corrected 3D bone model) is subtracted from the initial 3D model. The resulting product is a 3D template that represents a complete negative of the second model within the first model. This process can be carried out using libraries such as OpenGL or Vulkan, which are commonly used in graphics and game development, as well as libraries like CGAL (Computational Geometry Algorithms Library) used for geometric calculations (Fabri et al., 1999). The resulting template can be used to create a bone graft in the real world. For instance, this template can be filled with a biologically compatible material, which can subsequently be added to the patient's body. This technique is particularly useful when complex or customized grafts need to be created.

The process can be fully customized to meet the specific needs of a particular patient. For example, the dimensions of the template can be adjusted according to the patient's body measurements and the location where the graft is placed, and different materials can be chosen based on a specific patient's health condition and needs. For geometric calculations and manipulations, software libraries specialized in processing and analyzing 3D meshes, such as OpenMesh (Botsch et al., 2002), can also be utilized. Such a library allows for efficient storage and modification of mesh data, which is used to optimize the

precision and quality of the graft template. On the other hand, in the creation of the customized graft template, the selection and use of various biological and biocompatible materials are determined based on the patient's health condition and needs (Hutmacher, 2000). This process allows for the complete customization of the graft's structure and template, thereby ensuring a perfect fit for the area where the graft is placed and enhancing the patient's recovery process. In conclusion, the process of extracting the corrected 3D bone model from an initial 3D volume and thus creating a graft template is a significant step, especially for the production of complex or customized grafts. This approach can be fully customized according to the patient's body measurements and the location where the graft is placed and is anticipated to yield the best results.

CONCLUSION

The integration of advanced technologies such as 3D imaging, computer-aided design (CAD), and 3D printing has significantly improved the process of creating customized grafts, resulting in a better fit, more natural appearance, and reduced time and cost of surgery (Kung et al., 2020). Despite the significant advancements, there are still challenges associated with the use of customized grafts in cranioplasty. The process of designing and fabricating the graft can be time-consuming and requires specialized equipment and expertise (Tantisatirapong et al., 2023). The process addresses these challenges by leveraging artificial intelligence and machine learning technologies to assist in the design and modeling of grafts. This increases the speed and accuracy of the graft production process. Furthermore, the use of a Generative Adversarial Network (GAN) trained 3D modeling allows individuals who are not proficient in complex graphic programs to manage this process, providing significant advantages in terms of time, precision, and cost. Future work will focus on the development stages improving the design and fabrication process, developing new and better materials for grafts, and finding ways to reduce complications. In this way, the fields of medicine and information technology would be integrated to address the needs of patients in a novel way. This includes addressing operational needs that are not routinely encountered, 3D modeling processes that require anatomical knowledge and accuracy, and the need for meticulous personalized production. By integrating advanced technologies and leveraging the power of artificial intelligence, the process has the potential to improve patient outcomes and the field of personalized medical grafts.

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DRUG DISCOVERY WITH COMPUTER AIDED DRUG DESIGN METHODS

Okan AYKAÇ

- Affiliation: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas/TÜRKİYE
- Institution Information: Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Erzincan Binali Yıldırım University, Erzincan/TÜRKİYE
- ORCID: 0000-0002-7363-8801
- Mail: okanaykac@cumhuriyet.edu.tr

Burçin TÜRKMENOĞLU

- Affiliation: Department of Analytical Chemistry, Faculty of Pharmacy, Erzincan Binali Yıldırım University, Erzincan/TURKIYE
- ORCID: 0000-0002-5770-0847
- Mail: burcin.turkmenoglu@erzincan.edu.tr

Discovering a inovative drug molecule in the drug design is a very long and very complex process. In the latest studies to shorten this process, the role of Computer-Aided Drug Design (CADD) methods began to increase. CADD is one of the cheap methods that use large databases containing the theoretical models related to drug discovery. The CADD is used not only in the design of small molecules but also in designing large molecules. CADD is divided into two main parts as Ligand-Based Drug Design (LBDD) and Structure-Based Drug Design and forms the basis of molecular modeling. Due to the difference of algorithms used in molecular modeling methods; calculations made using different software. In this review, the current vehicles used in drug design emphasized by mentioning the recent CADD approaches.

INTRODUCTION

Nowadays, with the increase in problems such as the proliferation of diseases and the discovery of new drugs to cure these diseases, scientists have started to conduct research in drug discovery with faster and cheaper methods. The development, discovery, and design of new drugs is an interdisciplinary effort and a critical multi-step process (Szymanski et al., 2012). Recently, drug design processes computerized by scanning millions of molecules/compounds against target proteins. Computer Aided Drug Design (CADD) method has started to use at this point because it provides both cheaper and faster answers to scientists. Combining various computer tools to develop drugs forms the basis of CADD. CADD includes procedures such as computational chemistry, molecular modeling, molecular design, and balanced drug design (Muegge et al., 2017).

Drug Design

It has always been important to design new pharmacological agents that are both more resistant to older agents and with the idea of prolonging human lifespan. Many of these designs have been able to offer treatments for many diseases in the past. Thanks to these searches, pharmacological agents used in human and veterinary medicine have not ended. In what we call the computer age, it is unthinkable that drug design has not been influenced by the computer concept. It causes enormous economic losses during drug research and development, whether laboratory or clinical procedures. However, artificial intelligence and machine learning concepts, which make our lives easier everywhere in our age, have started to become faster and more effective when integrated into drug discovery. It is remarkable that investment in drug

screening with artificial intelligence and machine learning has continued to increase in recent years wherever there is Research and Development (Yousufi et al., 2022). The steps of developing a pharmacological agent consist of many steps, such as problem finding and etiological detection, HIT compound detection, validation of the detected HIT compound, precursor discovery and optimization of the precursor compound (Hughes et al., 2011). It has recently been added to the pharmacological agent development studies of artificial intelligence. When developed with the traditional method, the time spent with artificial intelligence will be further reduced (Muegge et al., 2017)(Charles, 1992).

It also reported that its molecule, known for its antibiotic activity, was developed with artificial intelligence by researchers at the Massachusetts Institute of Technology in Cambridge. With a similar news, Evotec has presented to the scientific world that clinical studies of an anticancer molecule designed entirely with artificial intelligence have begun (Yousufi et al., 2022).

Computer Aided Drug Design (CADD)

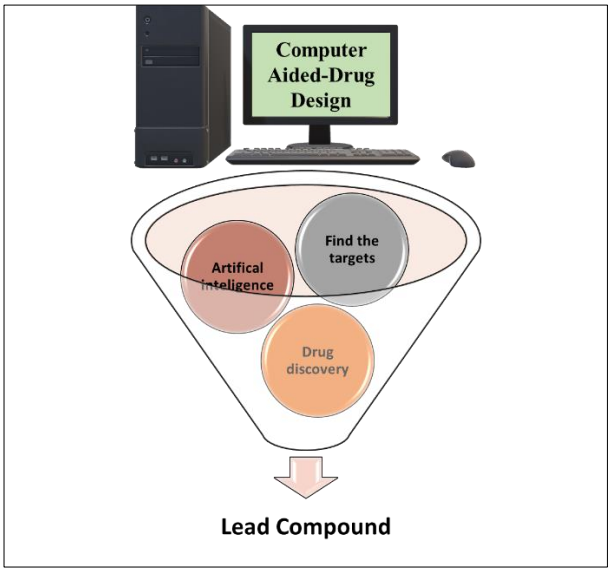

Figure 1. Basic concepts of CADD.

CADD is combined with conventional methods to elucidate the pathway of pharmacological activity and to design new agents that can be discovered. By supporting these activities, especially with SAR and QSAR studies, it provides a pharmaco-economic advantage in the development of

drug molecules both financially and temporally (Hughes et al., 2002). CADD includes topics such as computational chemistry, quantum chemistry, molecular modeling, molecular design (Muegge et al., 2017).

It is presented in Figure 1 that while lead compounds are found together with computer-aided drug design based on artificial intelligence (machine learning and deep learning), drug discovery is supported by the discovery of targets (Vemula et al., 2022).

Artificial intelligence can identify target compounds and precursors. In addition, it can quickly identify the drug target part and provides rapid optimization of the drug molecule. It can also aid in 3D structure forecast of a targeted protein, protein-protein connections, drug activity, and new drug design (Paul et al., 2021). Recently, ligand-based and structure-based approaches to computational chemistry have been used separately and in combination with drug discovery (Kizilcan et al., 2020).

The sub-sections of CADD which are Ligand-Based Drug Design and Structure-Based Drug Design are presented in Figure 2. The most important contribution of CADD is SBDD, including LBDD (Niu et al., 2022).

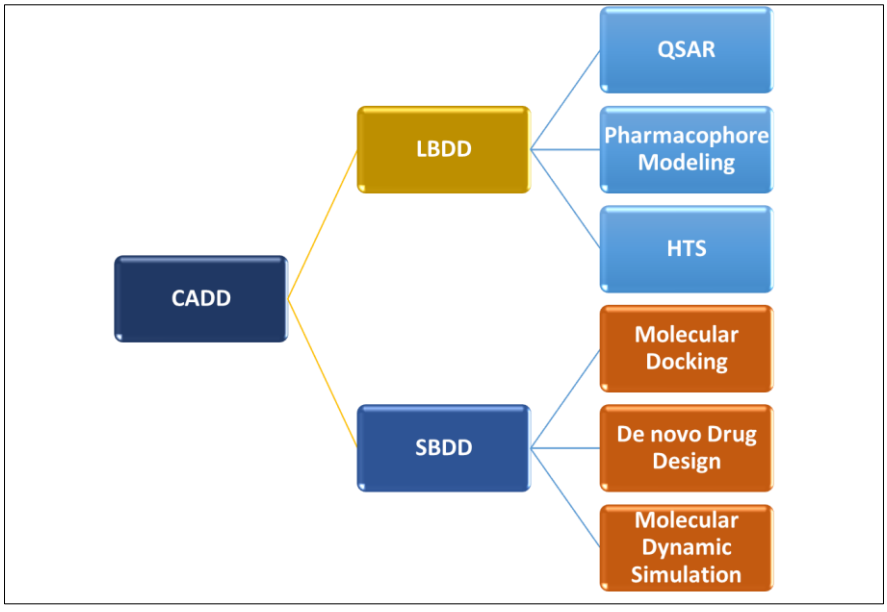

Figure 2. Sub-sections of CADD.

Ligand-Based Drug Design (LBDD)

Ligand-based drug design is a method used in the absenteeism of receptor 3D information but requires information of structures that bind to the biologic goal of interest. Quantitative Structure-Activity Relationships (QSAR) and pharmacophore modeling are very important and broadly used methods in ligand-based drug design. They can identify compounds that could be drug candidates and derive predictive models for optimization (Aparoy et al., 2021).

All the data acquired during the drug development process determines the method by which we will continue the process. Although the presence of 3-dimensional information about the biological target structure is not as strong as desired, data such as the presence of a drug molecule derivative specified for a disease affect whether we choose structure-based or ligand-based drug development approaches.

Quantitative Structure-Activity Relationship (QSAR)

After Fischer's key-and-key relationship (Wang et al., 1997) and the significant contributions of Hansch, Free, Fujita, and Wilson (Hansch et al., 1964), (Free et al., 1964) QSAR became widely used 40 years later, it has essentially made an important contribution to the drug discovery process. The concept of QSAR, which emerged in the early 1960s, has evolved very rapidly, particularly in the last decade, as an unprecedented advance of structural biology and computer capabilities. QSAR is based on the idea that compounds with similar physicochemical properties prompt similar biological effects on the basis of structure-specific drug molecules. The QSAR method is frequently used to establish a correlation between the structural and electronic properties of potential drug candidates and their binding affinity to a common macromolecular target (Liu et al., 2001).

It is based on considering the linear total contribution of different structural and chemical properties of a compound to its biological activity. It has been proven here that biological activity is in a linear relationship with transport and binding based on certain physicochemical properties. There are subtypes as 1D-QSAR, 2D-QSAR, HQSAR, Inverse QSAR, Binary QSAR, 3D-QSAR, 4D-QSAR, 5D-QSAR, 6D-QSAR. But the most used 3D-QSAR (Liu et al., 2022), (Gao et al. 2022), (Bi et al., 2022) and 4D-QSAR (Col et al.

2022), (Kizilcan et al., 2022), (Turkmenoglu et al., 2018), (Turkmenoglu et al., 2020) types are used.

Hop-finger introduced the fourth dimensional to the 3D-QSAR model in 1997 and coined the term 4D-QSAR analysis (Hopfinger et al., 1997). The difference between 4D-QSAR and 3D-QSAR is that multiple conformers are used, not single conformers. That is, the most stable compound is not the lowest energy conformer, but all conformers are considered in 4D-QSAR. While the most used programs in 3D-QSAR are CoMFA , CoMSIA, in 4D-QSAR generally researchers have their own software that considers multiple conformers.

Pharmacophore Modeling

The pharmacophore is also known as molecular properties that encompass the properties necessary for the biological activity of the drug. IUPAC has defined a pharmacophore as the sum of the steric and electronic properties necessary for a molecule to interact with a target and thereby provide biologic activity. It is a modeled version of a property responsible for the biological activity of a compound. This indicates that the pharmacophore concept is based on properties rather than chemical groups. Any component of a compound that exhibits properties associated with molecular recognition may constitute an example of a pharmacophore. To better understand how ligand-protein interactions occur, pharmacophore models are created. They can be used to design new molecules that meet pharmacophore needs and are therefore considered active. Molecular pharmacophore models; aromatic rings, hydrophobic properties, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), negative properties and positive properties can be expressed by their combinations (Muhammed et al., 2021).

In pharmacophore modeling in drug discovery, the congruence of certain points, groups, or domains in the molecule is analyzed. By aligning the molecules on top of each other, the so-called common drug-active group can be determined. For a set of derivatives with the same main structure, the pharmacophore group that the molecules have in common is revealed according to this analysis. For a series of compounds with different or the same structure, the rigid and active structure is selected in the fit method. The lowest energy structure of the effective reporter is formed, and then matching is done by determined the conformations of the precursor compounds that can

overlap with the precursor compound, and the common pharmacophore group can be found.

High Throughput Screening (HTS)

High Throughput Screening (HTS) Analysis under LBDD can screen several million compounds. Therefore, an effective computational process is required to analyze and use the data. Besides screening analysis, chemo-informatics is also important in choosing which compounds to screen. A large-scale HTS analysis consists of the main screening schematically testing 1-2 million compounds. Hits in the dose-response examine are followed to determine that the modulation has an appropriate sigmoidal curve. Hits are also screened in an experiment called orthogonal, in which another mechanically different screening technology is used to tidy out compounds that interfere with the screening technology. The whole process is highly dependent on the chemo-informatics input, starting with which compounds to screen for (Chen et al., 2018). There are a lot of libraries used when making HTS. The most used libraries are given in **Table 1**.

Structure Based Drug Design (SBDD)

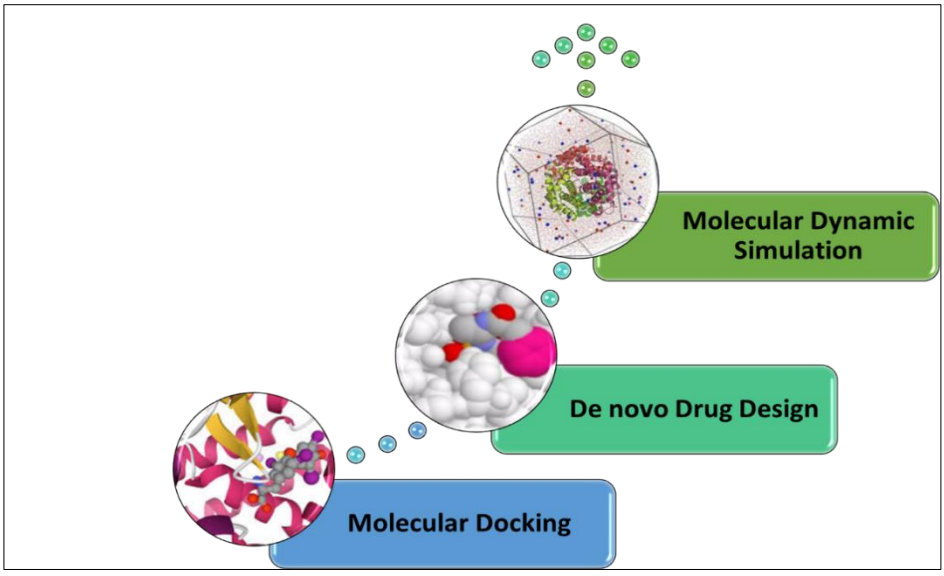

Figure 3. Sub-sections of the SBDD.

Structure-based CADD supports hit identification and optimization of medicinal chemistry by addressing two main tasks (Sledz et al., 2018). SBDD

is a method used to estimate how small molecules bind to the target and their binding affinity values. The subsections of the SBDD are presented in Figure 3.

Molecular Docking

Since the 1980s, a large number of molecular docking algorithms have been developed (Kitchen et al., 2004). The aim of molecular docking is to design a new therapeutic molecule that interacts more effectively with the target protein without knowing the ligands but knowing the receptor structure that serves as the target (Clark et al., 2010), (Lausted et al., 2014). Molecular docking, one of the most used methods in structure-based drug design, is a kind of bioinformatics modeling system that involves the interaction of two or more molecules to obtain a stable structure. Foretells the three-dimensional structure of any multifaceted based on the binding properties of ligand and target. Molecular docking models predict the optimized coupling conformer based on the total energy of the system. The main purpose of molecular docking is to form ligand-target complex with optimized conformation and less binding free energy intent. The net predicted binding free energy (ΔGBinding) is calculated via various parameters. Energy of the unbonded system, torsional free energy, dispersion/repulsion, desolvation, electrostatic, hydrogen bonding, total internal energy are among these parameters (Meng et al., 2011). It has been determined that many studies have been carried out in recent years with molecular docking, which is the most used method in drug design (Merde et al., 2022), (Merde et al., 2022), (Kuzu et al., 2022). In addition, while the binding affinity values are determined by molecular docking, the active binding site is also determined. This provides theoretically important information for the discovery of less toxic but more effective drugs that interact in the same way as reference drugs.

De novo Drug Design

Computational *de novo* drug design is an effective approach to construct new molecular structures with desired polytarget profiles at a very low cost and time-saving (Moreira-Filho et al., 2022). This modeling technique provides autonomous capability to automatically design new multitarget drug candidates using *de novo* drug design methods that emerge in the early stages of drug discovery (Meyers et al., 2021). The development of these models characteristically involves a two-step process. Firstly, a generative network is trained to construct syntactically credible structures

using a benchmark dataset of demonstrative structures. The model is then fine-tuned to produce only compounds with desired properties and used in drug discovery (Moreira-Filho et al., 2022).

Molecular Dynamic Simulation (MDS)

Molecular dynamics simulation is one of the structure-based methods used in drug discovery after molecular docking. It is a low-throughput procedure for the characterization of flexible binding sites in MDS and the accurate assessment of binding pathways, kinetics, and thermodynamics. Molecular dynamics virtual reality are some of the most integrated computations following virtual scanning simulations. Therefore, it is considered an advanced technique that complements docking (Sabe et al., 2021). They can also be applied previous to docking for conformational sampling and collecting on a protein molecule to accommodate the conformational dynamics associated with ligand binding (Menchon et al., 2018).

Softwares used in CADD

The softwares recently used *in silico* approaches are shown in Table 1. Some of the licenses of these programs are paid, some are free, and some are online. Since the algorithms and some basic equations used in all software are different, there may be differences in the results.

Table 1. The most used software in CADD methods.

CADD			
LBDD		SBDD	
QSAR	**HTS Libraries**	**Molecular Docking**	**Molecular Dynamic Simulation**
CoMFA	ZINC	Glide	Desmond
CoMSIA	ChEMBL	Gold	Discovery Studio
MOLFEAT	PUBCHEM	Autodock	NAMD
E-Dragon	NCI	Surflex-Dock	YASARA
McQSAR	DrugBank	CDocker	GROMACS
SYBYL-X	Enamine	LibDock	AMBER

CONCLUSION

With the increasing number and variety of new compounds discovered, the number of high-quality virtual libraries that can be boosted has also increased. *In silico* approaches have been used a lot recently to use the diversity in these libraries for drug discovery. Computer Aided Drug Design (CADD) forms the basis of *in silico* approaches to drug discovery. CADD is now used as a common alternative for support both experimental studies and preliminary studies. CADD has become a powerful tool for screening compounds that may be drug candidates, especially with current techniques. In the drug discovery process, which causes a lot of cost and time, savings have been started with this method. For this reason, in this review, which methods to use in case the target is known (SBDD) or not known (LBDD) are discussed in detail.

As a result, the importance of the methods that make up the sub-parts of CADD has been mentioned. It has been determined how much molecular docking in SBDD methods comes to the fore. In the LBDD method, the importance of QSAR to support the structural activity in the determination of the compounds that can be drug applicants, and the importance of determining the pharmacophore group in the determination of the active groups emphasized.

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