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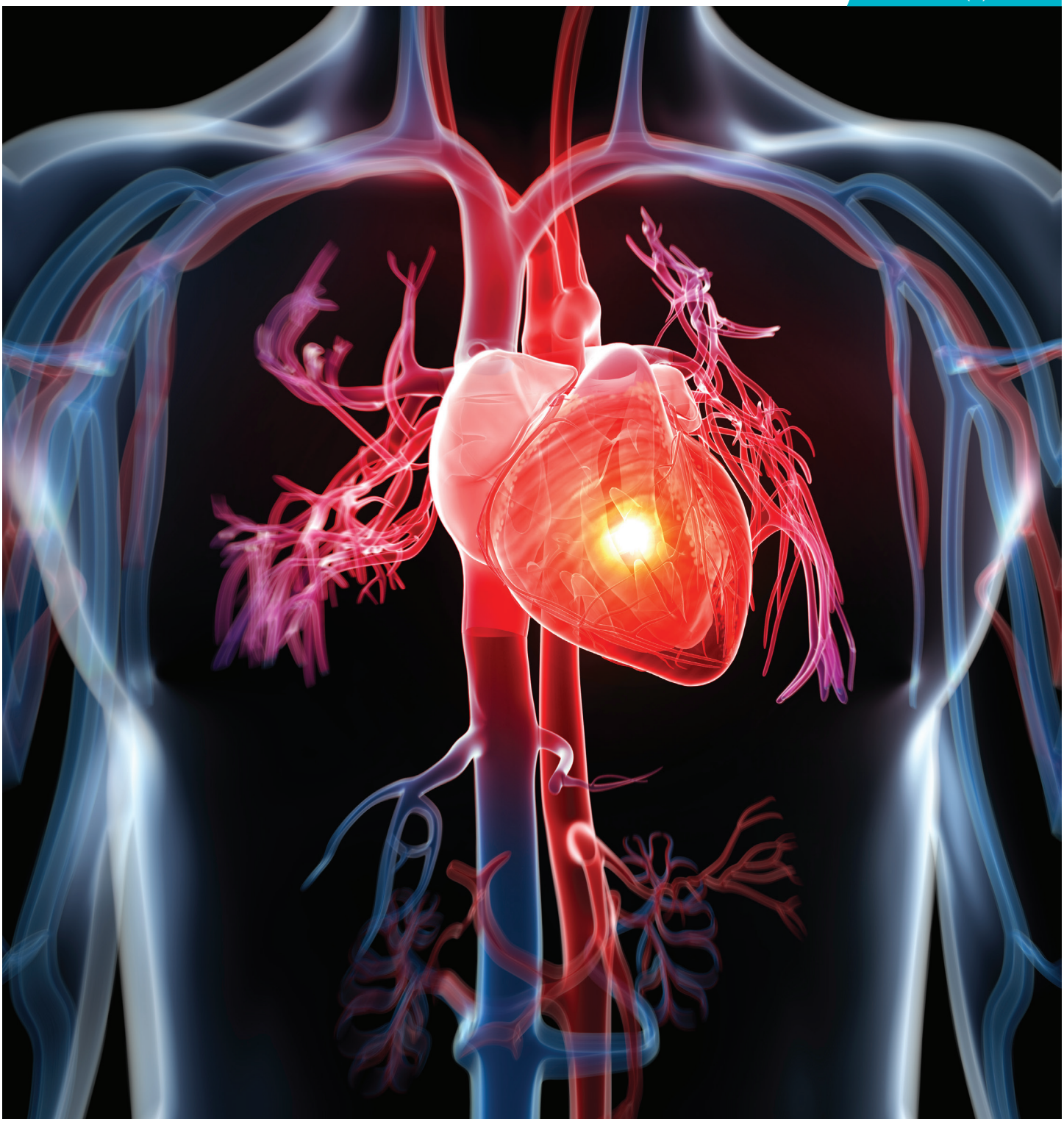

Features of the course of myocardial infarction in the elderly

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EDITORIAL

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Journal "Clinical Medicine of Kazakhstan" (ISSN 1812-2892) is a multi-field dedicated peer-reviewed medical journal. The main thematic scope – publication of materials on medical science and practice, education and healthcare organization. Joint Stock Company "National Scientific Medical Research Center" publishes the journal bimonthly in a year (in February, April, June, August, October, and December).

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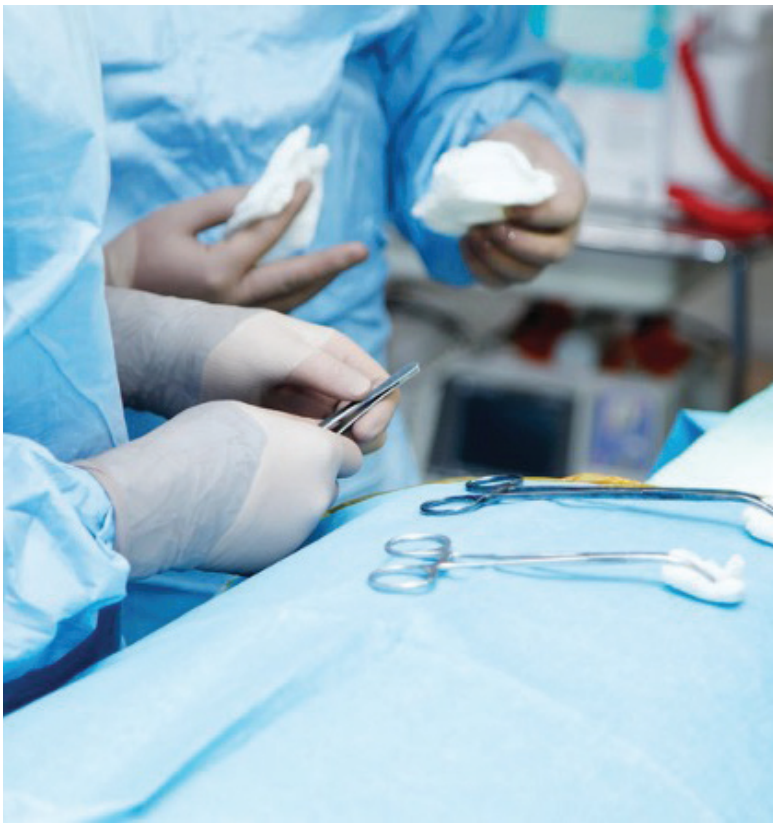

SURGERY AND TRANSPLANTATION

The key activities of these departments of NSMC are reconstructive surgery, transplantation, innovative minimally invasive approaches, microsurgical correction, cell-based therapy of various surgical diseases.
New types of minimally invasive surgical technologies, video-endoscopic and microsurgical techniques, mini-thoracoscopic operations, chemoembolization of tumors were implemented that fundamentally change the approaches to the treatment of many surgical diseases and reduce the time of hospitalization of the patients.

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Emergence of pediatric hospital medicine: A novel subspecialty in the Middle East

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Abstract

In this article, we give an overview of the hospital medicine model, which has recently been adopted by multiple healthcare systems. We will focus particularly on how pediatric facilities can transition to the pediatric hospital medicine model and reap its benefits.

Key words: pediatrics, hospital medicine, transition

Hospital Medicine Model

The term 'hospitalist' was coined in 1996 [1]. It described physicians whose primary area of expertise was managing the care of hospitalized patients. In the United States, the number of hospitalists began to rise in the late 1990s. The main driver behind this growth was an effort to achieve greater efficiency by reducing lengths of stay and decreasing care-related costs [2]. In the last two decades, hospital medicine has continued to grow at a rapid pace in the United States with some expansion internationally [3].

One of the major advantages of the Hospital Medicine model is that it allows for the growth of expertise in the inpatient setting for hospitalists, and in the outpatient setting for primary care physicians. Additionally, having a dedicated hospitalist physician improves care for higher acuity patients with multiple co-morbidities who require full time physician presence in the hospital [4]. Some of the challenges faced by outpatient pediatricians are the increasing complexity of patients, seeing more patients in less time while thoroughly documenting each encounter. Adoption of a hospital medicine model allows the outpatient pediatrician the time and bandwidth to overcome these challenges. Managing complex patients (eg. failure to thrive) at an inpatient setting facilitates a multidisciplinary approach due to easier access to different subspecialties and longer duration of patient encounter compared to the outpatient setting. One of the perceived disadvantages of this model is the loss of continuity of care by the primary physician when a patient is hospitalized. However, the rapid growth of hospital medicine suggests that the benefits of this model outweigh its weaknesses.

Pediatric hospital medicine model

Paralleling its adult counterpart, pediatric hospital medicine has had tremendous growth over the last two decades [5]. It is currently one of the fastest growing pediatric subspecialties in the United States [5]. This is driven by the rising complexity of pediatric patient population and need for dedicated teams and experts to manage the inpatient setting. Acknowledging the growth and impact of pediatric hospital medicine, it was officially recognized as a sub-specialty by the American Board of Medical Subspecialties in 2016 and the first certifying examination was administered in 2019.

Outside of North America, a traditional blended model of general pediatric care continues to dominate in most parts of the world, including the Middle East. In this blended model, hospitalized patients are managed by a team of junior physicians and residents who are led by a pediatric consultant. Following ward rounds, the consultant often proceeds to see patients in the clinics, while junior doctors continue to provide the ongoing hands on care for hospitalized patients.

Transitioning to the pediatric hospital medicine model

Transitioning to a pediatric hospital medicine model in the Middle East might be challenging as many pediatricians will be hesitant to let go of a large piece of their practice - whether it be inpatient or outpatient care. However, this can be mitigated by offering incentives to physicians who agree to make this shift and ensuring that the wards will be adequately staffed to avoid physician burnout. More importantly, it will be crucial to provide continuous medical education to inpatient physicians to enhance and update their clinical knowledge and skills.

After hospitals transition to this model by reallocating their staff either to the inpatient or outpatient setting, they should aim in the future to recruit only accredited pediatric hospitalists when staffing their inpatient units. This will support the growth of this model moving forward.

One example of a hospital that successfully transitioned to the pediatric hospital medicine model in the region is Al Jalila Children's Specialty Hospital in the United Arab Emirates. They can be used as a benchmark by hospitals that aspire to make such a transition. The implementation of this model should be strongly considered by healthcare authorities in the region, as it will to contribute to enhancing patient care and improving outcomes along various touch points within the healthcare system.

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A review of diagnosis of Duchenne and Becker muscular dystrophy

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Abstract

Duchenne muscular dystrophy (DMD and Becker muscular dystrophy (BMD) are progressive serious neuromuscular disorders. We have reviewed contemporary data on diagnosis of DMD and BMD. Searches were carried out from 2010 to 2020. This article discusses clinical signs, features in biochemical blood analysis, findings on instrumental investigation, various mutations causing DMD/BMD, indications for morphological examination of muscles available for setting up the diagnosis for children suspected of DMD/BMD.

Key words: Duchenne muscular dystrophy, Becker muscular dystrophy, diagnostic methods

Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are the most common forms in the structure of orphan diseases with damage to the neuromuscular system. They represent one of the important problems of clinical neurogenetics [1].

DMD is a severe type of muscular dystrophy with manifestation at the age of 2-5 years, progressive malignant course with a complete loss of motor activity at the age of 13-16 years and death, usually from heart or respiratory failure at the age of 20 years [2,3]. The disease is named after the French neurologist Guillaume-Benjamin-Amand Duchenne, who was the first person described it as "hypertrophic paralysis" in 1868. The incidence among newborn boys is 1 in 3,000-5,000 [4].

In 1955, German physician Peter Becker described “mild” type of muscular dystrophy, which was later named after him. This disorder occurs 6 times less often (1 case in 18,000-31,000), usually debuts later, the loss of motor activity is noted after 20 years, the life expectancy of patients can reach the fourth decade [5].

The diseases are caused by mutations in the dystrophin gene, the largest human gene located at the Xp21.2 locus [6]. At DMD this mutation results in a severe lack of dystrophin (<5%); at BMD there is an abnormal dystrophin formation or dystrophin deficiency. Dystrophin performs structural functions, protecting the muscle cell from tension at the time of contraction and relaxation of the muscle fiber. The absence of dystrophin causes impairment of skeletal and cardiac muscles, also the motor component of human activity is lost [7].

Since DMD/BMD is inherited in an X-linked recessive manner, it is usually affecting boys who have received the mutant X chromosome from a phenotypically healthy mother or mother with ‘mild” clinical manifestation [8]. In this case, their daughters will be carriers of the defective gene and will pass it to their male children - thus, the disease manifests only through a generation.

The prevalence of DMD and BMD in world populations is characterized by variability, the approximate average figure according to the meta-analysis of 31 studies is 4.78 (95% CI 1.94-11.81) and 1.53 (95% CI 0.26-8.94) per 100,000 men, respectively [9,10]. The results of an epidemiological study conducted in 6 American states (Arizona, Colorado, Georgia, Hawaii, Iowa and New York) showed a prevalence of DMD and BMD of 10,2 per 100,000 men aged 5 to 24 [11]. Also, the prevalence of DMD and BMD is higher than in the world, in Norway (16.2 per 100,000 men under 18 years old), in Canada (10.3 per 100,000 men under 24 years old), in France (10.9 per 100 000 male population) [12,13]. In some regions of the Russian Federation, the prevalence of DMD and BMD is different: in the Republic of Dagestan - 6.0 per 100,000 men, in the Samara region - 10.4 [14,15].

Currently, despite the developed diagnostic criteria, despite advances in diagnostic technology, the early diagnosis of DMD and BMD is a challenging issue. Patients consulted with many doctors before setting up the clear diagnosis [16].

Purpose: to review the literature on the diagnosis of DMD and BMD for the last 10 years.

Materials and methods

Searches were carried out from 2010 to 2020 in databases: PubMed and Google scholar. The search language: English and Russian. Key words: Duchenne muscular dystrophy, Becker muscular dystrophy, diagnostic methods. In both databases there were found 511 free full-text articles. Exclusion criteria: Studies published in non-English and non-Russian languages, studies published prior to 2010 and after 2020, animal studies, studies on epidemiology, clinical scales, treatment issues, life quality of patients. After reading of topic and abstract 32 articles were applicable for our aim. They were taken for analysis.

Results and Discussion

According to Clinical protocol of diagnosis and treatment on "Progressive Duchenne/Becker muscular dystrophy" of the Ministry of Health of the Republic of Kazakhstan dated by April 19, 2019, the modern diagnostic pattern of DMD and BMD includes the following methods: clinical manifestation, laboratory, instrumental, molecular-genetic tests and morphological examination of biopsy.

When establishing the DMD and BMD diagnosis the age of onset of the first clinical symptoms of the disease, the type of myodystrophic lesion (distal and/or proximal), the localization of atrophies, the presence or absence of pseudohypertrophies, fasciculations, sensory disorders, cramps, skeletal deformities, joint muscle contractures, the condition of muscle tone and tendon reflexes, disease course and progression of the disease is important [17].

As the dystrophin is localized in the central nervous system it's lack affects the brain's cognitive function. Almost one from three patients with DMD and BMD diagnosis has the cognitive impairment. However, this cognitive impairment proceeds without progression. There is a high incidence with autism spectrum disorders, obsessive compulsive disorder and attention-deficit hyperactivity disorder. Children might have delayed cognitive development, problems with reading, learning and speech delay [18,19]. These cause the intervention of multidisciplinary team (language specialists, neuropsychologists) to diagnostics and treatment [20].

Laboratory tests

The list of laboratory tests includes a biochemical blood test with the determination of the level of creatine phosphokinase (CPK), Alanine transaminase, Aspartate transaminase and lactate dehydrogenase (LDH) [21].

CPK is an intracellular enzyme that performs an energy function in the body. It is found in the greatest amount in the heart and skeletal muscles. Since the enzyme is contained inside the cells, so its increase in the blood indicates the destruction of these cells. An increase in CPK is the obligate early preclinical sign of DMD and BMD. An increase in the CPK level by 5 or more times is diagnostically significant. DMD is characterized by a significant increase in the level of enzymes by 10-100 times already in the early stages of the myodystrophic process [22].

Alanine transaminase (ALT) and Aspartate transaminase (AST) enzymes predominantly accumulate in hepatocytes, but are also largely concentrated in muscle cells. It is recognized that an increase in ALT and AST levels can signal the cytolysis of muscle cells, therefore, muscular dystrophies can lead to hypertransaminasemia [23]. Sometimes hypertransferasemia can be the only clinical and laboratory finding, more often it occurs with a parallel increase in CPK. Unlike other myopathies in DMD, there is a high degree of hyperenzymemia already in the early stages of the process development. Thus, the literature describes clinical cases of DMD and BMD with an increase in ALT to 477 IU/L, AST - to 497 IU/L [24].

LDH is an intracellular glycolytic enzyme that is involved in the reversible conversion of lactate to pyruvate and is found in most body tissues, and is most active in skeletal muscle. In diseases accompanied by tissue damage and cell destruction, the LDH activity in the blood increases, and therefore, it is an important marker of tissue destruction. Despite the fact that an increase in enzyme activity does not indicate any specific disease, its determination in combination with other laboratory tests helps in the diagnosis of muscular dystrophy. An elevated LDH level is not the obligate sign of DMD, whereas for BMD it is an early and diagnostically significant symptom. In a comparative analysis of 17 patients with DMD and 38 patients with PMD of unspecified etiology, the most significant differences between the groups were in the levels of enzymes of muscle breakdown (muscle cytolysis), namely, the LDH level was significantly higher by 4 times in patients with DMD [25].

One of the novels both diagnostic and therapeutic targets of DMD picture is the identification of miRNAs types in DMD. Its amount in blood and in muscle biopsy may be as biomarker of early disease or disease stage. miRNAs have correlation with muscle fibrosis due to partial connection to myogenesis [26].

Magnetic imaging and neurofunctional findings

Electroneuromyography (EMG) is a fairly simple but highly informative diagnostic method based on the registration and study of the bioelectric activity of the neuromuscular apparatus at rest and during its activation. EMG includes two main methods - stimulation and needle. In the diagnosis of DMD, stimulation EMG does not play a special role, needle EMG is more informative. It serves as the main research method for suspected DMD. The implementation of this technique allows us to identify the primary muscular type of changes in the motor unit potentials (decrease in the duration and decrease in the amplitude of motor unit potentials) and the spontaneous activity of muscle fibers (in the form of acute wave potentials, fibrillation potentials), indicating the degree of activity of the process in each specific muscle. The spontaneous activity recorded in DMD is always significantly pronounced, which distinguishes DMD from other hereditary primary muscular diseases. It is observed in the very initial stages of the disease, when, along with fibrillation potentials, acute wave potentials, and high-frequency discharges are detected [27,28].

The problem of involvement of the heart in the pathological process in DMD is well known [29]. Damage to the cardiovascular system (cardiomyopathy) develops in 73% of sick children, while the level of detection of cardiac disorders and the prevention of severe complications in the early stages are still very low [30]. Deficiency of dystrophin in cardiomyocytes leads to progressive atrophy and their replacement by fibrous tissue [31]. Cardiomyopathy for first time is diagnosed at the age of 6-7 years; by the age of 20, 95% of patients have it [32]. Patients with DMD are required to undergo electrocardiography (ECG) and echocardiography (EchoCG). The ECG is an important screening tool for detecting arrhythmias and conduction disturbances, ventricular hypertrophy or dilatation. EchoCG is considered the gold standard for diagnosing structural and functional disorders of the myocardium and contributes to the identification of cardiac pathology at the preclinical stage. Typical signs on the ECG are abnormalities in the heart rate,

rhythm and conduction of the heart, on the EchoCG - are signs of systolic dysfunction, left ventricular dilatation, myocardial hypertrophy, mitral regurgitation [33].

Ultrasound examination for assessing the condition of the muscles is attractive due to the absence of a radiation effect and relatively low cost. Also, the method is not invasive and allows with a high degree of probability (from 86% to 91%) to distinguish a healthy patient from a patient with neuromuscular pathology. Pathology in DMD and BMD is manifested by signs of muscle degeneration: replacement of muscle tissue with adipose or fibrous tissue [34].

Magnetic resonance imaging (MRI) has become the method of choice for muscle imaging due to the absence of side effects (ionizing radiation), good resolution and soft tissue contrast for full body scans [35]. For patients with DMD and BMD, the study can be used not only for diagnostic purposes, but also to assess the degree of muscle tissue degeneration in dynamics [36,37].

Genetic analysis

DMD/BMD are caused by mutations in the gene encoding dystrophin (DMD gene) [38]. The presence of genetic confirmation of the mutation is important for patients as it is important for the prognosis of the disease, neuropsychiatric involvement, genetic counseling and assessment of each patient's compliance with the criteria for new genetic therapies [39-42]. Determination of large mutations in the DMD gene in DMD/BMD is carried out firstly by the MLPA method. "Next-generation" sequencing technology and Sanger sequencing are proceeded when MLPA result is negative [43]. Next-generation sequencing is the way of choice as a DMD gene single-point detection technique, so some authors recommend to use it as routine strategy [44]. In accordance with international clinical guidelines, genetic testing for DMD/BMD is carried out in the presence of clinical signs of hereditary neuromuscular disease, as well as the patient's relatives and children. The biological material for research is DNA isolated from peripheral blood leukocytes, fibroblasts, chorionic villi, cultured amniocytes and other human tissues.

There are more than 3 thousand various mutations that might cause DMD, however the huge number of these mutations are localised within hotspots regions of the dystrophin gene. That is 6-7, 43-46 and 50-53 exons [45]. Genetic diagnosis is not easy due to the large size of the dystrophin gene (79 exons) and the complex spectrum of mutations. Large deletions (60-68%) and duplications (10-11%) are most common, but small mutations (20-30%) are also found [46,47].

The presence of the mutation is a molecular genetic confirmation of the clinical diagnosis of DMD/BMD and allows prenatal diagnosis in the family [48-50].

Morphological data

If genetic testing does not confirm a clinical diagnosis of DMD, the muscle biopsy sample should be tested for the presence of the protein dystrophin [51]. The indication for biopsy is the signs of muscle damage: muscle weakness, discomfort, cramps, pathological muscle fatigue; increased CPK level; myopathic lesion according to EMG data; differentiation between segmental demyelination and axonal degeneration; identification of inflammatory neuropathies; the presence of a systemic disease with myopathic manifestation. An open muscle biopsy is necessary if a differential diagnosis is performed, which considers DMD as one of the possible options among other muscular dystrophies, since it allows you to obtain the necessary tissue volume for further analysis. Needle biopsy does not require open surgery and may be warranted if DMD alone is considered. When examining muscle biopsy data, two types of tests are usually performed: immunohistochemical and immunoblotting analysis (a method for studying of protein antigens). These tests determine the presence or absence of dystrophin in quantitative form; with their help, it is possible to distinguish DMD from the milder form of myodystrophy - BMD. The morphological criteria of muscle pathology are: violation of the muscle fibers types distribution; change in the size of muscle fibers; violation of the structure of muscle fibers and their elements; pathological inclusions and mass formations in muscle fibers; pathological changes in skeletal muscle tissue in general. The histopathological peculiarities of DMD are: abnormal diameter variation of the muscle fibers due to atrophy or hypertrophy, focal necrosis, regenerative fibers and replacement of muscle tissue with fat and connective tissue (visually that is looks like pseudohypertrophy of muscles (usually calf muscles) [52].

Conclusion

To sum up, the diagnosis of DMD and BMD is complex. It includes the clinical manifestations, laboratory findings, genetic testing, instrumental tests and muscle biopsy. The majority of diagnostic technics are broadly available and feasible. The results of molecular-genetic analysis may correlate with the severity of clinical signs, it is valuable issue in confirmation of diagnosis and important in choosing of further pathogenetic therapy drug. Immunohistochemical and immunoblotting analysis of muscle biopsy data give the possibility to differentiate the number of dystrophin protein in order to diagnose the DMD/BMD or control the treatment with gene therapy in the future.

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The role of SHBG and LPL gene polymorphism in the development of age-related hypogonadism in overweight men: Literature review

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Abstract

Testosterone is the main male hormone responsible for the formation and maintenance of male sex characteristics and the sexual performance of men. With age testosterone levels decrease which is a natural physiological process. But the timing of age-related hypogonadism progress has individual differences. Physiological processes occurring in the body of an aging man are due to genetic, population and individual features of genes and their mutations leading to genetic polymorphism. Gene polymorphism is represented mainly by single nucleotide substitutions that are SNP (single nucleotide polymorphism). Sex hormone binding globulin (SHBG) and lipoprotein lipase (LPL) genes are important links in the synthesis and transport of testosterone in male body as well as in the development of androgen deficiency. This review discusses the role of polymorphic variants of SHBG and LPL genes in the early development of age-related hypogonadism in overweight men.

Key words: age-related hypogonadism in men, obesity, polymorphism of SHBG and LPL genes, overweight, erectile dysfunction

Introduction

The task of modern medicine implies diagnosis, prevention and treatment of diseases of male body and the capabilities of genomic medicine are aimed at completing this task. Testosterone as the main male hormone is responsible for maintaining male sexual characteristics and sexual capabilities of men [1]. With age, the level of testosterone decreases, but it is a natural physiological process [2,3]. There is a decrease in the testicles and libido, while adipose tissue increases [4]. But the time of occurrence of hypogonadism in everyone has individual peculiarities [5]. The physiological processes occurring in the body of an aging man are due to the genetic, population and individual characteristics of genes and their mutations. These mutations lead to genetic polymorphism that is represented mainly by single nucleotide substitutions-SNP (single nucleotide polymorphism). In recent years, the method of genome-wide association search (GWAS) has been widely used to search for marker-genes [6]. Both the synthesis of testosterone and its transportation to target cells is equally vital for maintaining a constant level for a male body. One of the important parameters for the transport of testosterone to target tissues is the level of globulin-binding sex hormone (SHBG) [2,7].

Sex hormone binding globulin (SHBG) is synthesized and secreted into the bloodstream by hepatocytes [8]. SHBG binds biologically active androgens, and regulates their bioavailability for target tissues [9, 10]. With an increase in the age of a man, there is a growth in the concentration of SHBG, that results in a decrease of free testosterone [11]. The change in the level of SHBG depends on its genetic variants [12]. A decrease in testosterone is always accompanied by excess weight, which is a predictor of obesity and metabolic syndrome.

Overweight and hypogonadism are mutually reinforcing conditions and there is no full explanation in medicine what is primary [13-15]. Some authors consider a decrease in testosterone to be secondary, since a decrease in body weight leads to a normalization of testosterone indicators [16]. Others believe that one of the reasons for the decrease in testosterone in obese patients is the activity of aromatase of excess adipose tissue [17-19].

Studies have proved that low concentrations of total testosterone are associated with an unfavorable lipid profile, which includes high levels of triglycerides and LDL and low levels of HDL [20].

In the metabolism of lipids, three key points such as absorption, transport and assimilation by tissues can be distinguished and assimilation begins with the action of lipoprotein lipase (LPL), which breaks down triglycerides into fatty acids and glycerin. Thus, LPL is one of the essential factors of lipid metabolism [21,22]. Testosterone also inhibits the expression of LPL in adipocytes, the main enzyme that regulates the accumulation of triglycerides in the fat cell. With a decrease in the level of testosterone, the number of adipocytes increases. This fact causes a violation of the metabolism of free fatty acids and excessive fat accumulation with a decrease in active muscle mass [23- 26]. In the presence of a LPL gene mutation hypertriglyceridemia and dyslipidemia develop, contributing to obesity, development of metabolic syndrome, coronary heart disease and hypertension [27,28].

Predictive medicine as the central direction of molecular medicine implies pre-symptomatic detection of persons with a high risk of developing hereditary diseases. However, the genetic risk factors for an early decrease in testosterone and factors that reduce it, such as obesity, diabetes mellitus and lipid metabolism disorders, have not been sufficiently studied and there are gaps in this direction. The search for new ideas, the optimization of existing scientific experience in the diagnosis of polymorphism of the genes of SHBG and LPL and the development of preventive measures for the age-related hypogonadism and obesity in men was the main reason to conduct literary review study.

The study is aimed at analyzing published works on the polymorphism of the genes of SHBG and LPL in the occurrence of early hypogonadism and obesity in men in Kazakhstan, in neighboring countries and in the world.

Searching strategy

To accomplish the task, we have carried out analysis of scientific publications in evidence-based medicine databases (PubMed, CochraneLibrary, ResearchGate, Webofscience, GoogleScholar, Paragraph Medicine, ScienceDirect).

Data sources

Inclusion criteria: studies of high methodological quality (meta-analyzes, systematic reviews, randomized controlled and cohort studies); also we took into account the publications on the results of case-control and cross-sectional studies with statistically proven findings in English and Russian.

Exclusion criteria: articles describing single cases and personal messages with no evidence base, abstracts, mass media and advertising articles.

Search depth: 10 years (2010 to 2020). 70 relevant papers reflecting the characteristics of the problem were accepted for the review content.

The keywords for the search: age-related hypogonadism in men, obesity, polymorphism of SHBG and LPL genes, overweight, erectile dysfunction.

As this was a systematic review, ethical approval and consent was not required to participate.

Findings

One of the most captivating works in the study of the genetic theory of early hypogonadism in men is the manuscript by Ohlsson (2011). This study identified two SHBG gene loci located at 17p13 (SNP: rs 12150660 and rs 6258) and at Xp22 (SNP: rs 5934505), which were significantly associated with serum testosterone levels. An r 6258 is the first reported SHBG polymorphism that affects the binding of testosterone to SHBG and the free fraction of testosterone and therefore may influence the calculation of free testosterone. But this study gives a modest result and explains the small percentage (0.6-2.3) inter-individual variability in testosterone levels. Additional variants of the sequence of alleles that affect the level of testosterone are probably not to have been identified and are yet to be discovered [29].

Based on Olson's experience, Chinese scientists conducted a similar study in the Chinese population. Yao-ping Chen (2015) and colleagues conducted a large-scale study in six regions of China: Hebei, Shanxi, Guangdong, Hubei, Jiangsu and Guizhou. The study group included 6,898 men aged 18 to 89 years. The aim of this study was to determine whether four SNP loci (rs12150660, rs727428, rs5934505, and rs10822184) are associated with low testosterone levels, hypogonadism, or obesity in the Chinese Han population. Obesity is one of the common causes of hypogonadism in older men [13]. According to this study, the frequency of the rs12150660 allele in the Chinese population is very rare, although in other studies this allele was correlated with the level of testosterone and SHBG in groups of European origin [29-32]. The results of this study have convincingly proved rs 5934505 to correlate with low testosterone levels in the Chinese population, as well as in Europeans, which creates the prerequisites for an early decrease in serum testosterone levels and the early development of age-related hypogonadism in men in the Chinese population.

In contrast to the European population, genetic analysis demonstrates that rs727428 is not associated with serum SHBG and testosterone levels in Chinese men. Rs10822184 significantly correlated with BMI in the Chinese population, which accordingly increased the risk of developing overweight and obesity. This study proves that loci rs12150660, rs727428, and rs10822184 differ between the Chinese and European populations. However, further large and functional studies are needed to confirm our results [33].

In 2019, Daniel Castellano-Castillo and colleagues studied the SHBG gene polymorphism (rs1799941) in young men. The study involved 212 men aged 30 to 45 years, with obesity (BMI above 30 kg / m2) and no history of diabetes mellitus. In the course of scientific research, it was found that the rs1799941 polymorphism in young obese and hypogonadal men was associated with SHBG levels and, therefore, could determine the free testosterone fraction. This study proves that rs1799941 of the SHBG gene determines the genetic factor for hypogonadism. It indirectly promotes obesity, which will undoubtedly be of clinical interest in the correction of hypogonadism in representatives with this polymorphism in the phenotype [34].

Guangfu Jin et al, in their studies identified a new 10q21 DNA locus that was associated with serum androgen levels using GWAS in 3225 European males, and confirmed two loci at 17p13 and Xp22 reported by Ohlsson et al. [29].

In addition to confirming the association of two known loci associated with serum testosterone levels (rs727428 in SHBG; rs5934505 in FAM9B), it was possible to identify a new locus JMJD1C in 10q21, which was associated with serum testosterone levels (rs10822184). There was also a way to prove that rs727428 was associated with serum DHT levels. However, some limitations of this study should be noted. First, 10q21, 17p13, and Xp22 variants account for only a small fraction of the total observed variance in serum testosterone and dihydrotestosterone levels. This suggests that there may be other genetic determinants of serum androgen levels that remain unknown. Second, the statistical power of this study has relative limitations, especially for assessing the association between SNP and prostate cancer risk, given that among 1,644 people in the placebo group, there were only 410 cases of prostate cancer and 124 cases of aggressive disease. Thus, future studies with a large sample size may be required in other populations to validate and extend our findings.

These results allow us to take a new look at the regulation of circulating androgen levels and may have clinical significance for androgen-related diseases [35].

Despite some progress in the personalized management of patients, there are many unclear points, in particular, the influence of genetic factors on the levels of reproductive hormones and the quality of sperm. Further studies of the genetic influence on the violation of reproductive physiology and the development of a personalized scheme taking into account the genetic profile of a man are needed to be conducted. In this direction, the work of Marina Grigorova (2017) is of special interest. The study has covered 578 men of reproductive age who were in an infertile marriage. All the men were recruited at the Andrology Hospital Center of the University of Tartu. All the study participants were born and lived in Estonia. In total, seven genetic variants in genomic DNA isolated from patients ' blood samples have been analyzed.

Of all the studied loci in the framework of our review, we were interested in a fragment of the SHBG study (rs1799941, rs727428, and rs6258). But the study did not reach statistical significance. Thus, the current data rule out a role for mutated SHBG in the predisposition to severe male factor infertility. Accordingly, none of the SNPs tested (rs1799941, rs727428, and rs6258) were significantly associated with testicular volume and total sperm count and concentration. This study excludes the role of SHBG polymorphism in the predisposition to male infertility [36].

Epidemiological studies have repeatedly found an association between low serum testosterone levels in men and subsequent development of central obesity, increased insulin concentration, metabolic syndrome, and diabetes. These studies are certainly associated with the LPL gene [37,38].

The state of hypoandrogenism in men is associated with insulin resistance that is a predictor of diabetes mellitus. According to the world literature review, the expected number of patients with diabetes mellitus by 2030 worldwide may reach 439 million; about 90% of these patients will have type 2 diabetes [39].

Sex hormone binding globulin (SHBG) is the main transport protein for testosterone and estradiol. However, recent research suggests that SHBG has additional biological significance. Low concentrations of SHBG are associated with an increased risk of type 2 diabetes mellitus [40]. Lifestyle and genetic factors may further contribute to the underlying physiological causes responsible for the pathophysiology of type 2 diabetes. More than 36 genes have been identified that are responsible for the risk of type 2 diabetes. All these genes account for only about 10% of the total genetic factors of the disease [41,42].

Tarhouny (2015) together with colleagues conducted a study of the relationship of SHBG polymorphism (rs6257 and rs6259) with the risk of diabetes mellitus and its effect on the level of sex hormones in the blood of men with proven type 2 diabetes. The study involved 185 male patients with type 2 diabetes mellitus observed in the Zagazig Diabetic Clinic, a control group composed of Egyptian men with normal fasting blood glucose levels. The owners of the rs6257 and rs6259 polymorphic variants had a significant decrease in SHBG, which led to a significant decrease in total testosterone levels and an increase in estradiol levels compared with the control group. This means that carriers of this phenotype have a high risk of developing type 2 diabetes mellitus [43,41].

This condition may contribute to a greater accumulation of visceral fat, which enhances insulin resistance and diabetes by increasing inflammatory cytokines [44]. Sex hormone binding globulin may be an important target for type 2 diabetes risk stratification and early intervention. This fact has been repeatedly confirmed by many authors [45-48]. Obesity and metabolic syndrome are often the result of hypogonadism and SHBG mutations, but this cannot be considered in isolation. Most of the LPL genetic defects cause hypertriglyceridemia and may be associated with obesity. Elevated blood triglyceride levels are one of the risk factors for cardiovascular disease [49,50]. At the moment, we cannot change a person's phenotype, but knowing his or her genomic data, we can predict the likelihood of developing a disease and effectively apply pharmacotherapy and diet therapy, which is the core principle of personalized medicine [51].

In this aspect, the study by T.B. Sentsova is worth considering. The study included 88 patients; the average body mass index (BMI) was 41.71±1.23. Since metabolic changes in obese patients were mainly associated with changes in lipid metabolism, the dynamics of blood biochemical parameters was assessed for various polymorphic variants of LPL genes before and after the use of a standard version of a low-calorie diet. When studying the dynamics of blood biochemical parameters of carriers of various polymorphic markers of the LPL gene, it was found that a pronounced positive effect of diet therapy in obese patients was observed in carriers of the polymorphic C/C variant of the LPL gene (Ser447Ter) [52,53]. The level of lipid metabolism in the blood is determined not only by genetic factors, but by the lifestyle that leads to overweight and obesity.

Jung-A Pyun et all conducted a study tracing the influence of lifestyle factors on lipid levels in Koreans with LPL polymorphism (rs263, rs271 and rs328). In the course of the study, it was found that the carriers of this polymorphism, with the consumption of calories in food (fats) had higher HDL levels. In representatives who did not have this polymorphism, this effect was not observed. Carriers of the same genotypes with alcohol consumption showed higher triglyceride levels. Given these data, it can be assumed that the appropriate lifestyle can be recommended in accordance with the type of LPL polymorphism for each person [54, 55].

Considering that LPL is related to overweight and obesity, in our search we have selected all genetic studies concerning LPL mutation in the relationship of lipid pathology and liver and pancreas diseases as a factor affecting BMI and testosterone levels in the blood of men.

Obesity is the most common predictor of metabolic

syndrome associated with hypertriglyceridemia. A similar relationship can be traced in the relationship of type 2 diabetes.

P. Han (2020) in his scientific research has identified three mutations of the LPL gene (c.162C> A, c.835C> G and c.1322 + 1G> A) in two unrelated Chinese patients with extremely rare and severe uhypertriglyceridemia. The functional analysis of the identified mutations has been carried out. As a result of this mutation of the LPL gene, partially or completely non-functional lipoprotein lipases are formed, which are unable to catabolize triglycerides into chylomicrons. Consequently, there is a gradual and progressive increase in chylomicrons, which leads to hypertriglyceridemia, diabetes mellitus, and the development of metabolic disorders [56]. These studies have been repeatedly carried out at different times by different authors [57-63].

It is a favorable fact that there are developments in gene therapy with an adeno-associated viral vector (AAV) for a lipoprotein lipase LPL (S447X) mutation in lipoprotein lipase deficiency. This pathology is characterized by severe hypertriglyceridemia and the risk of recurrent pancreatitis or other complications [64].

Lipoprotein lipase (LPL) plays a central role in lipoprotein metabolism, hydrolyzing the main fragments of triglycerides and circulating and low density lipoproteins (LDL). Researcher Rebhi L. (2012) also evaluated the effect of three polymorphisms HindIII, PvuII and Ser447Ter in the LPL gene on the lipid profile in Tunisian patients with coronary heart disease. Patients with genotypes HindIII TT, PvuII TC, and Ser447Ter had high levels of triglycerides, total cholesterol, and low density lipoproteins in plasma. The result of the study suggests that the HindIII polymorphism is considered as a marker of predisposition to coronary stenosis. Thus, there is an association between variants of the LPL gene and high levels of triglyceride, total cholesterol and LDL cholesterol, as well as low levels of HDL [65,66]

Violation of lipid metabolism requires a comprehensive study. It is worth mentioning that the weight loss after bariatric surgery affects the parameters of lipid metabolism the changes of which are due to genetic factors causing obesity. Sarzynski and his collaborators in Sweden conducted a 10-year patient monitoring of 1,771 Swedish obese patients after gastric ligation or bypass gastric anastomosis. The study demonstrated that the rs283 polymorphism was closely related to the baseline level of high-density lipoprotein (HDL-C) cholesterol in patients, and the level of HDL-C in the GG genotype groups was higher.

The amount of changes in high-density lipoprotein (HDL) cholesterol caused by weight loss might be of genetic character. We examined associations of eight candidate genes identified by genome-wide association studies with HDL-C at baseline and 10 years after bariatric surgery in a Swedish study of obese patients. None of the SNPs were significantly associated with changes in HDL levels associated with weight loss.

Thus, our results show that genetic variants contributing to the total level of HDL-C in persons with stable weight have little effect on individual variations in HDL-C changes in response to weight loss caused by bariatric surgery [67].

Lipoprotein lipase (LPL) plays a role in lipid homeostasis, and their gene mutation can be considered as prognostic genetic markers of metabolic syndrome.

In the study we aimed at assessing the possible associations of polymorphisms and LPL PvuII (+/-) with metabolic syndrome and signs (waist circumference and body mass index).

In the total sample of variants, representatives with a polymorphic variant of LPL (PvuII) had a large waist circumference and an increased BMI. The study results were featured by the significant effect of the LPL gene on HDL-C levels in the male population.

According to the results obtained, a mutated variant of the LPL gene can be factors of impairment of lipid status and predisposition to obesity, contributing to the development of metabolic syndrome, especially in men [68].

Similar to the previous research, the influence of the relationship between polymorphic LPL (Pvu II and Hind III) and carbohydrate consumption on the components of the metabolic syndrome in representatives of the Korean population has been studied (Kim Y., 2013). The study reveals that carriers of the polymorphic LPL variant (Hind III) have a high risk of developing metabolic syndrome and arterial hypertension. That undoubtedly needs to be taken into account during dynamic observation of this category of patients [69].

Lipoprotein lipase controls the distribution of fatty acids in body derived from circulating triglycerides, and plasma LPL concentration is closely related to intra-abdominal fat distribution.

Rui-Rui Gao investigated the effect of exercise on lipid and glucose metabolism. The researcher targeted at studying the effect of exercise on lipid metabolism in obese adolescents in the Han population with LPL gene polymorphism (rs283). In adolescents with the GG genotype, there is a more noticeable decrease in the percentage of intraperitoneal fat, insulin resistance and triglycerides during exercise. This fact indicates the possibility of early correction of lipid metabolism disorders by changing the lifestyle [70].

Conclusion

Analyzing the literature, we came to the conclusion that a genetic predisposition may contribute to the early onset of hypogonadism, overweight and obesity. But despite the great advances in decoding the human genome, there are no clear criteria in the genetic diagnosis of the early development of hypogonadism. Age-related hypogonadism is becoming an increasingly relevant condition, making it a public health problem. Its causes and physiological consequences at the individual level are still elusive. However, genetic predisposition at the individual level is the basis on which various other lifestyle and nutritional factors act, leading to its early development. Obesity does not occur without the presence of vulnerable genetic factors. Indisputably, further research in this area is needed to understand the pathogenesis of development in various population groups.

Summing up, we note that today there is no unified approach to processing the results of scientific research in the field of studying genetic predisposition, and, moreover, there is no unified assessment of the feasibility of using various preventive methods and its effectiveness in assessing the risk of hypogonadism. Therefore, a comprehensive and balanced approach is required both for the search for disease markers and for assessing their suitability for accurate risk prediction.

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Features of the course of myocardial infarction in the elderly

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Abstract

Cardiovascular disease is a major contributor to morbidity, mortality and quality of life in people aged 60 and over. However, this age group of patients was not sufficiently included in large studies, in this regard, the management of elderly patients is an urgent problem in modern medicine.

The purpose of this review is to analyze literature data on the characteristics comorbid pathology and senile asthenia as a predictor of unfavorable course and outcomes of acute myocardial infarction in patients 60 years of age and older.

To analyze the literature, we searched for information on this issue in PubMed/MEDLINE, PMC, Web of Science, Scopus, The Cocrane Library.

Recent research data show that there are plenty of risk factors for worsening the course of AMI in patients aged 60 and over. The most important of them are considered to be high comorbidity, multivessel lesion of several pools, the presence of senile asthenia. All together lead to difficulties in diagnosing myocardial infarction, to forced polypharmacy and in some cases refraining from early invasive strategy, which worsens the course of the disease, increases the duration of hospital treatment, leads to frequent complications, thereby affects the prognosis of the disease and leads to the development of early disability in patients 60 years of age and older

In the vast majority of elderly patients, the development of acute myocardial infarction occurs against the background of a high prevalence of comorbid pathology, which in turn accelerates the development of senile asthenia and its progression.

Key words: acute myocardial infarction, advanced age, senile asthenia, comorbidity, unfavorable prognosis

Introduction

According to WHO statistics cardiovascular diseases (CVD) are the main cause of high levels of morbidity, disablement and mortality globally, causing negative effects in economics and social development. 31% of all deaths are caused by cardiovascular diseases [1].

To date coronary artery disease is one of the most challenging problems in developed countries, especially the most dramatic type of CVD - myocardial infarction. According to Kazakhstan's official statistics in 2019 the mortality rate from cardiovascular diseases was 163,14 per 100 000 of population, of these 58,25 per 100 000 accounts for coronary artery disease. Mortality from acute myocardial infarction (AMI) constitutes 8% of patients discharged from hospital [2].

The majority of patients with AMI are elderly and senile individuals. Age range of patients' data classified by the WHO: elderly age from 60-75 years old, old age from 75-90 years old, centenarians over 90 years old. Thus, the doctors most frequently deal with management of this cohort of population in clinical practice. As it is known this age group is often underrepresented in large randomized clinical trials, hence, management of elderly and senile patients is a pressing issue in medicine. Elderly and senile people constituted as low as 6,7% out of 719 922 patients from 593 published trials from 1966 to 2000. This suggests that more data must be gathered on management of elderly and senile patients with acute coronary syndrome (ACS) to provide precise clinical recommendations [3].

Higher life expectancy is leading to an increase in elderly population worldwide. Thus, in 2012 the percentage of elderly people out of 7 billion people was 562 million people (8,0%). By year 2015 this number increased to reach 8,5% or increased by 55 million elderly people [4].

According to statistics the percentage of elderly people will reach 25% of total population by year 2050. This tendency proves that the ageing of the population will be observed in a future [5]. Kazakhstan's statistical data shows similar tendency: in 2014 the proportion of elderly people was 6,8% of total population, this number increased to 7,5% by the end of 2018. As observed there was an increase of proportion of elderly age group in 4 years period. According to demographic data the proportion of elderly people in Kazakhstan is expected to double by 2050 from 7,5% to 14,1% [6].

Taking into account the annual increase of the proportion of CVD and the ageing of population there is a need to further investigate the problem of myocardial infarction in Kazakhstan and worldwide.

The purpose of this review is to analyze of literature data on the characteristics of risk factors, comorbid pathology and senile asthenia as a predictor of unfavorable course and outcomes of acute myocardial infarction in patients 60 years of age and older.

To analyze the literature, we searched for information on this issue in PubMed / MEDLINE, PMC, Web of Science, Scopus, The Cocrane Library. The search depth was 13 years: from 2008 to 2020.

Unfavorable risk factors for worsening the course of AMI in patients over 60 years of age

The incidence and mortality from AMI among elderly and senile remains high. Considering increase in elderly population this tendency is likely to progress [7,8].

According to R.D.Lopes et al., patients aged 65–79, 80–84, 85–89 и 90 years and older have shown the one year mortality rate of 13,3; 23,6; 33,6 и 45,5 % respectively after first myocardial infarction [9].

Patients of advanced age have numerous risk factors for a worse outcomes in AMI. Most important risk factors are presence of comorbidities, multivessel stenoses, fragility and compromised metabolism. This causes challenging diagnostics of myocardial infarction, polypragmasy and leads to unfavourable outcomes of the disease.

Impact of high comorbidity on AMI

The course of the main disease in patients older than 65 years is usually accompanied by comorbidities. As it is known, patients aged 65-76 years have a comorbidity rate of 62%, patients older than 85 years have a 82% comorbidity rate [10, 11]. Similar data were reported in a number of publications, including the research of M. Fortin, et al, W.A. Rocca et al [12, 13]. Therefore, there is an increase in structure and severity of comorbidities with age.

As noted from many literary sources, among the most common comorbid pathologies in AMI patients, arterial hypertension, hyperlipidemia, type 2 diabetes mellitus, chronic kidney disease, chronic heart failure are often found. In the structure of comorbid pathology, chronic obstructive pulmonary disease and gastric ulcer should also be distinguished [14-17].

As it is noted in most publications, the presence of comorbidities has a negative impact on disease outcomes lowering life expectancy for a number of years compared to individuals without comorbidities [18].

Recent studies showed that patients with myocardial infarction have high comorbidity rates, which is a predictor of unfavourable outcomes of the disease [19]. Most patients with myocardial infarction acquired more comorbidities with age. In other words, most patients with AMI and high comorbidity rates were of advanced age. Thus, these patients require close attention as they have an increased risk of death, stroke, prolonged hospitalisation and development of new myocardial infarctions with complications [20-23].

Another study has shown that patients of advanced age with combination of myocardial infarction and arterial hypertension have a 50% increased 5-year mortality rate, type 2 diabetes also constitutes to a worse outcome [24].

Clinical portrait of patients with AMI and high comorbidity rates frequently shows painless course of a disease, symptoms are somewhat unclear and atypical and mimic the clinical course of a comorbidity rather than the main diagnosis. This makes diagnosis challenging and leads to erroneous hospitalisations to secondary hospitals significantly delays the initiation of reperfusion therapy [25-27].

It is therefore obvious that comorbidities significantly worsen general health status of an elderly patient with myocardial infarction leading to difficulties in diagnosis due to atypical presentation of a disease, worsens prognosis and quality of life, and leads to high mortality rates which are up to 82% according to certain data. The predictive factors of a fatal outcome are systemic inflammatory reaction due to compromised microcirculation and inflammatory phenomenon [28, 29].

Multifocal atherosclerosis as one of the predictors of an unfavorable outcome of AMI

According to research patients of advanced age with AMI have a combination of two major vascular catastrophies. Patients with haemodynamically significant atherosclerosis of coronary arteries have a 30% rate of brain vessels involvement. This leads to a significantly worse prognosis in patients with coronary artery disease in general population (survival rate is about 50%). Atherosclerosis of coronary arteries is diagnosed in 30—60% of patients with acute ischemic cerebrovascular accidents . Multifocal atherosclerosis is a common pathogenetic factor of myocardial infarction and ischemic stroke [30].

Interrelation of high comorbidity and senile asthenia

In management of patients of advanced age, it is important to keep in mind the presence of senile asthenia which is associated with high comorbidity rates.

NICE recommendations suggest detection of senile asthenia as a method of establishing patients with high comorbidity rates who may benefit from individualized treatment approach [31,32].

Senile asthenia (of frailty, R54 ICD-10)- is an age related syndrome in which the decline of physiologic reserves of the organism leads to a decline of multiple system functions, this in turn increases the susceptibility of an elderly patient to multiple factors and high invalidization, morbidity and other unfavorable outcomes. High comorbidity rates constitute to development and progression of senile asthenia. However, early detection of senile asthenia may lead to the involution of this state and enables better management of a patient [33].

Along with age, risk factors for the formation of senile asthenia are the presence of several comorbid pathologies, chronic inflammation, polypharmacy, decreased physical activity, decreased immune function, malnutrition, depression, frequent hospitalizations, social factors (unfavorable relations with relatives, low income, marital status, low level education) [34,35].

The vast majority of patients with senile asthenia syndrome have a number of concomitant diseases. The relationship between senile asthenia and cardiovascular diseases has been determined [36].

The role of senile asthenia in the course of AMI

According to recent studies, senile asthenia increases the risk of CVD and death by 2.5-4 times [37].

Senile asthenia is a complex clinical syndrome of high susceptibility to stress factors, that results in a decline in multiple system functions. This leads to partial or total imbalance between chronological and biological age. Individuals with low functional ability and physiological reserve are at higher risk of homeostasis imbalance in case of a stress, particularly myocardial infarction [38,39].

Accordingly, the severity of senile asthenia in patients with ACS increases the degree of interleukinemia of proinflammatory cytokines and neuroimmunoinflammatory mediators of inflammation in the blood serum, which adversely affects the course of ACS. The interaction of senile asthenia and ACS forms a neuroimmunoendocrine imbalance, which leads to further progression of senile asthenia syndrome [40]. High levels of natriuretic peptide (BNP) and interleukin-6 (IL-6) are markers of short-term and long-term unfavorable outcome in AMI [41].

Risk stratification of elderly and senile patients with AMI

In daily clinical practice, the cardiologist does not carry out the identification of frailty in elderly and senile people with ACS, but this is very important for determining unfavorable predictors of this disease [42].

Cardiologists and doctors of other specialties must acknowledge the role of senile asthenia in patients of advanced age hospitalized with ACS. This needs to be fulfilled in aforementioned age group of population. It is important to study elderly people more and establish treatment strategies and methods taking into account the senile asthenia [43].

There is an evidence gap in management of patients with various comorbidities and the treatment of this cohort of patients remains mostly empiric.

The development of a database with information on how to manage patients with multiple comorbidities is needed for doctors to provide an evidence based approach in treatment of this cohort of patients [44].

The aims of treatment in patients with senile asthenia are maximal maintenance of the functional status, self-sustainment and quality of life [45], which will provide positive effects on medication tolerance, compliance and prognosis [46].

Over the past few years there is a surge in effort oriented on comorbidity minimization and reduction of its negative effects. The main goals of these activities are to detect and further manage high-risk patients. Risk stratification is of major importance for an optimal management and strategy selection in treatment and diagnosis as well as prevention of unfavourable outcomes in patients of elderly and senile age [47, 48].

Conclusion

The totality of the elderly is not the same, the prognosis is influenced not only by age, but also by the presence of chronic diseases, senile asthenia syndrome and multivessel disease in several pools.

To date, the presence of a comorbid pathology in a patient is quite relevant. Many diseases included in the structure of comorbidity have common risk factors and pathogenetic links with coronary artery disease, which significantly affects the course, outcome and development of possible complications, worsening the prognosis of patients with AMI.

In most elderly patients, AMI develops against the background of a high prevalence of comorbid pathology, which in turn, together with age-related changes, accelerates the development of senile asthenia and its progression. The presence of an unfavorable combination of risk factors, high comorbidity and senile asthenia leads to difficulties in the diagnosis of myocardial infarction, forced polypharmacy and, in some cases, abandonment of an early invasive strategy, leads to an increase in the duration of inpatient treatment, the development of disability, an increase in complications after surgical interventions, and requires high costs for diagnosis, treatment, rehabilitation of AMI.

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Assessment and treatment requirements of public hospitals to radiation emergencies

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Abstract

Radiological emergencies present unique challenges to the public health care system and carry the potential for major disruptions to clinical care. This review aims to present, first a brief guide of the main clinical and laboratory diagnostic tools for the assessment of the absorbed dose in cases of radiological emergencies and second, the best treatment options for acute whole body and local radiation syndromes. Clinical and laboratory state-of-the-art biodosimetry tools, therapies for acute radiation syndromes according to the severity of the radiation sickness and isotope-specific preparedness medications as counter-measures for internal contamination are herein proposed as the necessary stockpile of public hospitals against severe radiological accidents.

Key words: radiological incidents, radiation emergencies, biodosimetry, acute radiation syndromes, radiation treatment

Introduction

The public exposure to ionizing radiation poses a tremendous and complex challenge to the health system [1], due to the degree of hospital preparedness, the availability of special resources and the technical skills from the involved personnel required to confront this kind of emergency [2]. Among the requirements to cope with radiation emergencies, public hospitals need high-end diagnostic tools and treatment options. Both these items will be described beneath, according to the data of relevant bibliography and the long occupational experience of the authors.

Radiation Dose Assessment

After either external exposure to radiation or contamination with radionuclides, the radiation dose received by the victims should be assessed for optimal medical treatment, prognostic advice and epidemiological analysis. This is particularly important, because in whole body absorbed doses of more than 1 Gy, dose-dependent deterministic effects, like radiation sickness or hematological syndrome, may appear in the following weeks or months to the victims. On the other hand, in absorbed doses of less than 1 Gy, chronic stochastic effects, like cancer or genetic abnormalities may develop and the potential risk of that perspective needs to be calculated to establish continuing follow-up of these high-risk individuals [3]. Estimation of absorbed dose may be accomplished mainly by dosimetric readings, physical reconstruction of the exposure conditions, clinical symptoms and signs and specific laboratory measurements.

Radiation biodosimetry is a continually developing field, which focuses on specific clinical and laboratory biological markers, whose values express known relationship to the absorbed dose of ionizing radiation [4]. The field of radiation biodosimetry starts from hospital triage and emergency treatment and extends to mass screening and managing large-scale population exposures to unknown levels of radiation [5, 6]. From the hospital-care point of view, radiation biodosimetry is based on clinical symptoms and laboratory measurements; both will be presented underneath.

Clinical biodosimetry

The most common clinical symptom after exposure to high doses of ionizing radiation is vomiting; the time to onset of vomiting and the severity of the symptoms are related to the dose rate and the total dose received. Generally, the higher the absorbed dose, the faster is the onset of vomiting and the heavier the severity of symptoms [7, 8]. As an example, vomiting onset in less than 4 hours after irradiation corresponds to whole body absorbed dose of more than 2 Gy and it is strongly indicative that acute

hematologic syndrome will develop in about 30% of victims; if however, vomit occurs within one hour, the exposure is expected to be lethal in more than 90% of victims, with an estimated whole body absorbed dose of more than 6 Gy. Though non-specific, because other pathologic or psychogenic causes of vomiting need to be excluded, the time to onset of vomiting remains the most sensitive clinical sign to assess absorbed dose [3].

As regards local organ injury, skin is the most typical example of dose related damage; erythema will appear in local doses of more than 3 Gy; desquamation, blister formation and ulceration will need doses in the range of 10-20 Gy, whilst necrosis will emerge in even higher doses. In all cases of skin damage the time of onset is expected within 2-3 weeks [9].

Laboratory biodosimetry

C-reactive protein and serum amylase were two of the first biochemical serum markers of whole body irradiation [10]. Through the years laboratory biodosimetry has largely expanded into the fields of genomics (changes in genome expression investigated by use of recombinant DNA technologies and bioinformatics) and proteomics (changes in proteomic profiles of cytokines), to estimate the level of individual radiation exposure. In real practice however, the two major laboratory techniques are the lymphocyte depletion kinetics and the cytogenetic biodosimetry.

Lymphocyte depletion kinetics (LDK)

Lymphocytes are the most sensitive blood cells in irradiation and show a rapid and predictable decline after exposure to radiation. The total lymphocyte count should be measured every 6 hours for the first 2 days and then periodically. A fall of more than 50% in the first day suggests a potentially lethal absorbed dose [11]. A similar pattern is also observed in the medium term, showing practically zero lymphocyte count at 6 days after exposure in lethal doses (> 8 Gy) [9].

Cytogenetic biodosimetry (CB)

Cytogenetic biodosimetry refers to a range of sophisticated laboratory techniques to quantify ionizing radiation doses absorbed by exposed individuals [12]. The most important cytogenetic biodosimetry tools are:

a. Dicentric chromosome assay (DCA); it is based on the principle that radiation causes DNA double strand breaks, thus producing an accurately dose-dependent number of dicentric chromosomes in peripheral blood lymphocytes. DCA is the optimal biodosimetry technique when blood samples are collected in less than 2 months after irradiation [13], it is standardized by ISO at all reference biodosimetry laboratories [14] and is alone recommended as the reference technique by the IAEA [15]. DCA requires significant technical expertise and is time consuming, requiring at least 3-5 days after sampling, thus making non-applicable dosimetric requirements on an emergency basis, but is very sensitive and specific even at doses as low as 0.05 Gy [16].

b. Cytokinesis-block micronucleus (CBMN) assay is another accurate laboratory biodosimetry tool, being easily automated, simpler and technically less demanding than DCA. It is sensitive to absorbed doses above 0.3 Gy, an adequate value to discriminate victims of radiological emergencies from individuals requiring continuous surveillance [15, 17].

c. Fluorescence in situ hybridization (FISH) assay; it retrospectively identifies radiation-induced chromosomal translocations, which unlike DCA and CBMN, can persist decades after the exposure. Though of limited availability and accuracy, as well as of higher cost, the FISH technique is superior to the previous assays in samples older than one year [18, 19].

d. Less common laboratory biodosimetry assays are the premature chromosome condensation and the electron paramagnetic resonance assays, with the second used in dry specimens, e.g. teeth, bones and fingernail clippings. Furthermore, it has been applied in longitudinal studies of severe radiological exposures from accidents or atomic bomb survivors [3].

In addition to clinical and laboratory biodosimetry tools, absorbed dose of internal radiological contamination may be assessed by surveying activities with specific radiation counting devices and probes from the whole body and specific organs, as well as from urine, faeces, pulmonary and gastric lavage washings, nasal swabs and wound dressings. Whole body counters are much more sensitive to detect internal and residual external contamination compared to portable detectors. And yet, various online algorithms for absorbed dose estimation based on clinical and biological data are available from the Radiation Event Medical Management website [20].

Depending on the availability of the equipment, the type of the assay applied, the number of patients to be measured and logistics, laboratory dosimetric results may require several days till weeks to be available [21]. Since biodosimetry resources are crucial for the mitigation of radiological incidents, standardized and reproducible assays among laboratories are essential for accurate biodose assessment. Many countries have established biodosimetry laboratories which apply standardized techniques as an integral part of their national radiation protection strategy. Albeit DCA is intrinsically time-consuming and available only in selected certified centers worldwide, there is currently an urgent need for revising existing biodose laboratory tools, by shortening the analysis time (e.g. with computer-aided microscopy), by interconnecting with similar laboratories through the web and by improved documentation and reporting [22]. A broader applied, user-friendly software tool to assist in the comprehensive evaluation and interpretation of clinical, dosimetric and therapeutic data of radiation victims has been developed by the U.S. Armed Forces Radiobiology Research Institute and is called Biodosimetry Assessment Tool (BAT) [23]. Nonetheless, although the utility of approaches using only clinical and routine laboratory findings to stratify victims into risk groups during large radiological incidents is still unclear [24, 25], time to onset of vomiting and the absolute lymphocyte count are universally considered the most practical clinico-laboratory combination to rapidly estimate the absorbed dose during the first days after exposure [7].

Treatment requirements
Treatment of Acute Radiation Syndromes

Acute radiation sickness (ARSI) is defined a serious illness occurring after irradiation of the entire body with high doses in a short time. Typically, the first symptoms of ARSI are non-specific, including nausea, vomiting and diarrhea. The first symptoms start within hours to days after irradiation and last for hours up to several days; the victim may then feel healthy for some time (latent period), till he/she will become sick again with more severe symptoms, even seizures and coma. The third stage may last for hours up to months [26]. ARSI is manifested with various clinical syndromes called acute radiation syndromes (ARS); their severity is dose related,

as follows [27]: Haemopoietic syndrome, in doses more than 2-6 Gy, gastrointestinal syndrome, in doses more than 6-8 Gy and neurological syndrome, in doses more than 12-15 Gy. The clinical pattern of each syndrome is divided into three phases: a prodromal phase, occurring during the first few hours after exposure, a latent phase that shortens with increasing total dose and dose rate, and a manifest clinical phase that will result either in recovery or death [28]. Depending on whole body absorbed dose victims can be stratified into those who:

a. Will not need further medical intervention;
b. Could benefit from supportive treatment;
c. Require aggressive treatment;
d. Cannot be saved.

After an international consensus meeting in 2005, a biodose clinical grading system has been established, as a unified basis for individualized medical management of victims from radiological accidents, based on clinical data from 70 such accidents, including 800 victims. That system is called METREPOL (Medical Treatment Protocols for Radiation Accident Victims) and assesses acute neurovascular (N), hematologic (H), cutaneous (C) and gastrointestinal (G) damage for early prognosis of multi-organ failure. The severity grade for each index ranges from 0 (no damage) to 4 (irreversible damage). The final scoring is expressed in alphanumeric form e.g. N2H3C4G0 [29].

Dosimetric considerations

When speaking of partial-body, fractionated or chronic irradiation, outcome prediction is challenging due to difficulties in partial-body dosimetric calculations, variations of damage among organs and activation of the body's repairing mechanisms which mitigate the initial radiobiological impact. Due to the complex nature of radiation injury no single therapy or medication will provide benefit against all aspects of it; combined and specialized supportive therapies will probably be required in more patients than initially expected to gain significant prognostic improvements [30].

Experience from severe past radiological incidents indicates that supportive care alone can increase survival probability [28]. More specifically, the LD50 values in victims with no or minimal medical treatment have been estimated to 4.5 Gy in low rate irradiation and 3.29 Gy in high rate; when best supportive medical treatment is applied, respective values get almost double, to 7.81 and 6.13 Gy, respectively. However, longitudinal survival rates are much less impressive; the twelve-month survival rate from acute whole body irradiation with more than 6 Gy approximates zero, due to a systemic syndrome affecting the internal organs and mostly the cardiovascular system, called radiation-induced multi-organ dysfunction (RiMOD) [3].

Treatment of high absorbed whole body doses

Patients having received doses lower than 2 Gy, are generally not expected to manifest ARS and may be provided home-care instructions and close outpatient follow-up. In doses higher than 2 Gy, after initial triage, decontamination and diagnosis of ARS, treatment modalities include [11]:

a. Symptomatic relief, i.e. analgesia, antipyretics for fever and common anti-emetics for nausea and vomiting; however in doses higher than 3 Gy most patients will require serotonin receptor antagonists.

b. Fluid administration, to maintain fluid balance and well-cooked, low-residue enteral feeding, free as possible from infection sources, to preserve calorie balance and gut function.

c. Acute radiation exposure definitely compromises the immune system of radiological victims and polymicrobial septic infections tend to accompany radiation injuries [31]; thus antibiotics should be prophylactically administered when the neutrophil count is lower than 500 cells per microliter, conjugated with prophylactic or therapeutic anti-viral treatment.

d. Blood product transfusions will be required in radiological victims suffering non-irreversible myeloablation. Blood may be transfused either as whole, or as blood products (red cells and platelets).

e. Granulocyte-colony stimulating factors (G-CSFs) have the potential to accelerate bone marrow recovery after whole body irradiation [32] and act as radio-mitigators when combined with additional supportive care and blood product transfusions. G-CSFs have been successfully applied in radiation victims of the Goiânia, San Salvador, Soreq and Nesvizh accidents [33-36]. Despite many extensive reviews in recent bibliography, only two of these growth factors, Neupogen® and Neulasta® have been approved till now by U.S. FDA for treatment of ARS [3].

f. Stem cell transplants, including umbilical cord blood and bone marrow transplants, may be required in victims of large-scale radiological incidents who will suffer irreversible myeloablation. Till 2005, only 31 patients worldwide have undergone allogenic haemopoietic stem cell transfusion (HSCT) after severe radiological accidents [37] and no more thereafter. Although bone marrow transplantation (BMT) is the only alternative when spontaneous marrow recovery is not possible [38], the medical data gathered from the accidents at Chernobyl and Soreq in Israel [39, 35] strongly suggest that due to age and histocompatibility constraints, BMT should be considered only for victims having received uniformly distributed whole body doses of 8 till 12 Gy, with no serious cutaneous or conventional injuries and with no severe internal contamination.

g. Cutaneous radiation injury (CRI) is the injury caused by significant irradiation of the skin. It may result either alone, or combined with the systemic symptoms of ARS or conventional injuries, such as thermal burns or blast trauma. The clinical symptoms vary and the onset is usually delayed. Treatment of CRI is notoriously challenging, involving specialized assessment of plastic surgeons and radiation oncologists as well as lifelong follow-up in severe cases due to the very long healing time of deep lesions. More specifically, CRI treatment is largely symptomatic, requiring general supportive measures against dehydration, hypothermia, infections and nutritional deficiency. In the acute phase of skin irradiation, continuous washing with cool water may reduce initial inflammation, followed by antihistamine, non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroids, or even opioids in severe cases with intense pain, to achieve adequate analgesia. Infection is a major complication often conjugated with compromised hematopoietic system and requires careful application of antiseptics and antimicrobials. Skin necrosis requires autologous cutaneous grafts whenever possible, although in extended or combined injuries this may be inapplicable [3].

In case of a severe radiological incident requiring tertiary hospital management, both non-contaminated and decontaminated patients are triaged for estimation of the severity of radiological deterministic effects, either of ARS or subclinical radiological effects:

a. Patients with subclinical deterministic radiological effects have typically received a dose of less than 2 Sv, are all in ambulatory state and without clinical symptoms, or they present

mild signs of radiation sickness. They usually need no Intensive Care Unit (ICU); rather they are admitted in the general ward of the Hospital, wherein they undergo radiobiological estimation of stochastic and chronic effects and future health risks and they are also enrolled in long-term health follow-up protocols.

b. Patients with mild or moderate ARS (1st - 2nd degree) are ambulatory and they are admitted in either the general ward of the Hospital, or in general ICU, wherein they receive broad-spectrum antibiotics, blood or blood components transfusion and possibly, anti-neutropenic agents, e.g. colony stimulating factors.

c. Patients with severe ARS (3rd - 4th degree) are urgently admitted in specialized ICU, or by case in a Burn Care Unit (BCU), wherein apart from previous therapies, they receive total parenteral nutrition, growth factor therapy, and typically require stem-cell allogenic transplantation (Table 1).

Table 1 ARS therapies according to severity of the syndrome

	ACUTE RADIATION SYNDROME THERAPIES			
THERAPY	1st degree	2nd degree	3rd degree	4th degree
Ambulatory – General ward admission	√			
General Intensive Care Unit		√		
Broad-spectrum antibiotics		√	√	√
Blood components transfusion		√	√	√
Colony Stimulating Factor (CSF)*		√	√	√
Specialized Intensive Care Unit			√	√
Total Parenteral Nutrition			√	√
Plasmapheresis			√	√
Growth Factor Therapy			√	√
Cytokines therapy (Interleukin-3)			√	√
Stem-cell allogenic transplantation				√

* Anti-neutropenic agents (e.g. Filgrastim)

Internal contamination medications

Internal contamination refers to internal dispersion and incorporation of radionuclides by the human tissues and organs via inhalation, ingestion or any other route of biological absorption depending on their chemical and biodistribution properties [40]. Their depletion from the body varies largely and is measured by the effective half-life of each radionuclide, ranging from a few days (e.g. one week for radio-iodine) to many decades (e.g. 50 years for plutonium). Although it is unusual for internally absorbed doses to provoke ARS, the ongoing irradiation of tissues and organs increases the risk for stochastic effects, mostly of malignancies [21]. The key point for maximum effectiveness of internal contamination countermeasures is therapy commencement with radionuclide-specific medications, called radiological antidotes, as early as possible. Antidotes administration should be based on chemical and metabolic behavior of each radionuclide, the route of exposure and absorption, availability of resources and individual patient status [41]. The main categories of radiological antidotes clinically approved for human use are the following:

Potassium iodide

Potassium iodide it is an effective blocking agent against radioiodine uptake from the thyroid gland after a radiological emergency releasing radioactive iodine (e.g. a nuclear plant accident). Normal thyroid accumulates avidly about 30% of the radioiodine and blocking of the gland should start not longer than 4 hours after exposure [42, 43]. The recommended dose is a 130 mg received orally for adults, half that dose for children 3-18 years, one quarter for infants 1 month to 3 years and one eighth for new-born infants. Potassium iodine stockpiling for immediate post-exposure mass prophylaxis is a prudent public health measure, albeit the presence of this agent in large quantities carries a potential risk for unintentional or deliberate misuse [44].

Prussian blue

Prussian blue (potassium ferric hexacyano-ferrate); it is a decorporation agent that binds the radionuclides of cesium and thallium, increases their excretion through the feces and prevents their reabsorption from the gut into the blood [45]. The proposed optimum dose in case of, e.g. contamination with Cs-137 is 3 gram per day, administered in fractionated doses at regular intervals. Therapy with this antidote may last for long periods of time, even months, in severe cases, like the case of the accident in Goiânia, Brazil, where 46 individuals in total received orally this medication in various doses and timing [33]. Importantly, the effective half-life of Cs-137 was reduced on average to one third, thus rendering this agent an excellent radiological antidote for Cs-137, even when administered several days after contamination. Nonetheless, stockpiling of this agent before a radiological event in hospitals remains again challenging [33].

Decorporation chelating agents;

Decorporation chelating agents; they eliminate specific radionuclides from blood circulation and body tissues by increasing the biochemical turnover and excretion by the kidneys. Chelating agents are more effective when applied soon after exposure and before incorporation of radionuclides by bone, liver and other target organs [46]. Diethylene-triamine-penta-acetic acid (DTPA) complexes with calcium or zinc have been successfully used in the treatment of internal contamination with soluble salts of various radioactive heavy metals [21, 41, 47]. Considerations regarding the commonest radioactive heavy metals requiring antidotes:

a. Uranium; industrial grade or depleted uranium is weakly radioactive and the chemical toxicity of soluble uranium salts in kidneys is of greater concern compared to its radioactivity [48]. Calcium or zinc DTPA chelates are not effective in the treatment of uranium toxicity, unless administered the very first hours. A rather better option is sodium bicarbonate treatment, which produces a less nephrotoxic complex that is also more readily excreted [49].

b. Americium; after absorption it is deposited mainly in bone and liver, intimidating bone marrow suppression and hepatic failure [50]. DTPA chelates increase urinary excretion of americium by 50 times; calcium chelate is considered more

efficient in the first hours, but zinc chelate is better tolerated.

c. Cobalt; it is an essential metal of most human tissues, mainly concentrated in the liver. DTPA chelates are of limited effectiveness; penicillamine is rather preferred in cases of significant absorption of radioactive cobalt, though urinary excretion is expected to be increased by only one third [51].

d. Polonium; the extremely dangerous isotope polonium-210 is one of the few radionuclides able to cause symptoms of lethal ARS within a week after ingestion; death comes as a result of multi-organic failure after oral ingestion of only 1 microgram of polonium-210, which is regarded as lethal dose, whilst ARS will appear sooner when higher doses are intaken [52-54]. Sulfhydryl-chelates, like DMSA (succimer; dimercaptosuccinic acid) may help in polonium poisoning by increasing renal excretion of polonium, though not undoubtedly [21].

Concerning medications for internal contamination, radiological antidotes may be enough for contamination with low levels of absorbed dose, but alone they are not adequate treatment against high level exposure. Potassium iodide and Prussian blue are included in WHO's list of essential medicines required in a basic health system [55]; decorporation chelates though, are not. In any case, sufficient amounts of antidotes should be immediately available in mass-casualties situations [56]. Thus, radiological preparedness of a hospital requires stockpiling of adequate quantities and types of such medications; several consensus guidelines for radiological antidotes stockpiling have been proposed [57]. These should be added in the preparedness list for hospital medications against radiological accidents (Table 2).

Table 2 Main preparedness medications list against radiological accidents

Radionuclide	Antidote	Main Reference	Efficacy
I-131	KI	[58]	+++
Cs-137	Prussian blue	[9]	+++
Am-241	Ca/Zn-DTPA	[50]	++
U-235/238	NaHCO3	[48]	+
Co-60	penicillamine	[51]	+
Po-210	DMSA	[52]	+

Conclusion

The complex medical nature of radiological emergencies poses unique challenges to the public health care system and carries the potential for major disruptions to clinical care. Comprehensive preparedness requirements of public hospitals as described in this study are essential features for proper national and global radiological response. Various aspects of advanced radiological preparedness, including clinical and laboratory biodosimetry, along with treatment of acute radiation syndromes, external irradiation or internal contamination are herein also presented, along with concrete clinical proposals. These aspects imply a novel preparedness doctrine regarding more sophisticated radiological response planning in the public health sector. Ultimately, by further refining the currently available clinical and laboratory diagnostic tools and by providing specific therapeutic protocols and isotope-specific medications, the health management of radiological incidents and emergencies in public hospitals is expected to be further promoted.

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Alternative ways to correct poor glucose metabolism in patient with diabetes mellitus

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Abstract

There is an annual increase in the incidence of diabetes recorded worldwide. The existing measures of prevention and multimodal treatment of the disease have not yet brought the desired results. A promising field is bariatric (metabolic) operations used in obese patients, which also improve glucose metabolism in the case of concomitant diabetes mellitus of both types 1 and 2. At the same time, there is a certain contradiction and understatement regarding the mechanisms that lead to remission of diabetes mellitus, regardless of weight loss. One of the anatomical effects of bariatric procedures is the accelerated release of nutrients into the distal segment of the small intestine, which leads to stimulation of enteroendocrine cells and increased secretion of incretins (GLP-1, PYY, etc.). The experiment investigates these mechanisms by the operation of ileal transposition. Further study of the ileal transposition effects using different models of type 1 and type 2 diabetes, accompanied both with and without obesity, may contribute to a more detailed understanding of the triggering and supporting mechanisms of increasing glucose tolerance in the struggle against this disease.

Key words: diabetes mellitus, metabolic surgery, ileal transposition

Introduction

Diabetes mellitus is a chronic, progressive, widespread disease, with a steady upward trend worldwide. Various aspects of diabetes are well described: morbidity, early and late complications of the disease, impact on the quality of life and health care costs, mortality, etc.

The International Diabetes Federation (IDF) assessed the overall prevalence of diabetes mellitus: if in 2011, it was diagnosed in 366 million patients, then by 2030, it is projected to be found in 552 million patients. According to WHO, in 2014, the number of patients was 442 million adults, compared to 1980, when the number of people suffering from this disease was 108 million [1,2].

Every year, huge funds are allocated for the treatment of diabetes. In total, $760 billion was spent worldwide in 2019 to combat this disease [3].

It is shown that patients with diabetes mellitus have a high risk of disability and cardiovascular diseases, compared with people who do not suffer from this pathology. Moreover, this risk tends to increase over time since the lack of good metabolic control, which is evidenced by constantly increased levels of glycosylated hemoglobin (HbA1c), inevitably leads to complications: diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, as well as macrovascular problems [4].

The coronavirus pandemic has forced a new insight into diabetes mellitus as a life-threatening situation when combined with COVID-19. There are indications that diabetes is not a risk factor for COVID-19 but it has an aggravating effect on its course and outcome [5].

Treatment of patients with diabetes, of course, leads to an improvement in their condition and gives a certain economic effect [6]. However, physiological and, therefore, the most affordable measures, i.e. changing the lifestyle and diet, do not achieve significant long-term results [7] and drug therapy only causes compensation in 30% of patients, while remission is achieved only in a minimal number of patients [8].

Therefore, the relevance of the problems of diabetes mellitus today remains high. Efforts to solve these problems should probably be aimed at searching for new methods of treating and preventing the development of diabetes using advanced technologies.

Effect of Bariatric Operations on Glucose Metabolism.

Recent studies have revealed and, subsequently, confirmed the positive effect of bariatric operations in patients with type 2 diabetes mellitus (DM2), both with and without obesity. Bariatric operations (baros = weight) is a surgical procedure performed on the gastrointestinal tract in patients with pathological obesity. Such operations are often referred to as metabolic operations because of their positive effects: weight loss and improved metabolic control, especially in patients with DM2. Obviously, these effects have allowed several authors to consider a bariatric surgery as an alternative to pharmacological treatment, which can help to correct overweight, control hyperglycaemia, and achieve remission of the disease [9-20]. A number of studies have shown that surgical methods were successful and improved the condition of patients with diabetes mellitus of type 1 (DM1) [21-23] (Table 1).

Table 1 Bariatric surgery and diabetes: literature review results

Procedure	Procedure	Following time (years)	HbA1c	(%)	Remarks
Adams et al.[15]	418 RYGB (93 T2DM) 417 nonsurgical obese control (106 T2DM 321 population-based control (92 T2DM)	6	< 6.5	62% complete remission	Better control of bypass than nonsurgical group Mean BMI 45.9
Arterburn et al.[16]	4434 RYGB	5	< 6	68% complete 9% partial	Retrospective cohort
Cohen et al.[17]	66 RYGB	6	< 6.5	88% complete 11% partial	30 < BMI < 35
Lakdawala et al.[18]	52 RYGB	5	< 7	58% complete 38% partial	30 < BMI < 35 96% improvement Of metabolic status
Heneghan et al.[19]	52 RYGB, LSG, LAGB	5	< 6.5	44% complete 33% partial	Mean BMI 49 ± 8.7
Sultan et al.[20]	95 LAGB	5	< 6	40% complete 40% partial	Mean BMI 46.3
Scopinaro et al.[16]	312 BPD	10	ND	97%	
Pontiroli et al.[16]	23 BPD 78 LAGB 37 control	5.5	ND	100% 66% none	
Marceau et al.[16]	1356 DS (377 T2DM	7	ND	92%	

BPD - biliopancreatic diversion, LAGB - laparoscopic gastric band, RYGB - Roux-en-Y gastric bypass, LSG laparoscopic sleeve gastrectomy, DS duodenal switch, ND not defined.

A meta-analysis conducted by Zh. Khorgami et al. (2019) showed that within 2 years, 138 patients out of 263 who underwent surgery experienced remission of type 2 diabetes, compared to 7 out of 200 who received medication only. There was also a more significant decrease in HbA1C, serum glucose, increased HDL, and decreased triglycerides [24].

Bariatric operations that are the subject of the analysis are divided into restrictive (sleeve gastrectomy (SG) and regulated gastric banding (GB), malabsorption (intestinal bypass anastomosis), and combined, as well as combined/restrictive and malabsorbing (Roux-en-Y gastric bypass (RYGB) and biliopancreatic bypass with or without a duodenal switch, BPD or BPD-DS).

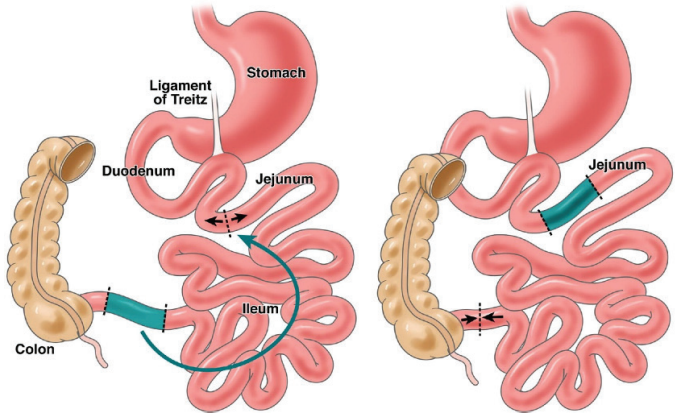
Studies have found [13,14] that remission of DM2 occurs in 66%, 45%, 80-85%, and 95% of patients after SG, GB, RYGB, and BPD-DS, respectively. The mechanism of remission of DM2 after bariatric surgery is still debated.

Thus, the most effective procedures for the induction of remission in type 2 DM are RYGB and BPD-DS [19-23]. Both procedures involve the exclusion of the duodenum from the digestive process and this mechanism was assumed to be required the effect of the operation, which has been confirmed by experimental studies by Rubino and Marescaux [30]. However, another anatomical effect of these operations is the accelerated discharge of partially digested nutrients and their contact with the distal segment of the small intestine, the ileum, which contributes to the secretion of peptides of intestinal origin involved in glucose homeostasis [9].

To study the role of the distal segment of the ileum in RYGB surgery, the ileal transposition operation is used in the experiment [31], and the authors have shown that the procedure itself induces remission of type 2 diabetes and weight loss without a component of disabling the duodenum [32], but this opinion is controversial.

The ileal transposition (Figure 1), as an experimental operation, has found its origin in the work of H. Koopmans et al. (1982), who, while studying the effects of a jejunoileal bypass, particularly, a decrease in food intake, suggested the presence of an endogenous signal from the distal segments of the ileum in response to stimulation by food masses. In order to confirm this assumption in the experiment, the authors performed a resection of 10-20 cm of the distal part of the ileum in rats, followed by its movement on the neurovascular bundle to the proximal segments of the jejunum. The procedure was called the ileal transposition, and for the first time, there was a decrease in the amount of food consumed, body weight, glucose, triglycerides, and cholesterol levels with a preserved length of the small intestine [8].

Figure 1 - Scheme of Ileal transposition



Some clinical studies combined the ileal transposition with gastric bypass surgery or sleeve gastrectomy [33-36]. During a study of the metabolic effects of the ileal transposition in combination with elevating sleeve gastrectomy (DSG) in 159 patients with obesity and DM2, Celik et al. found a decrease in the average body mass index (BMI) from 39.33 to 25.51, the average fasting glucose level from 189.9 to 123.5 mg/dL, and the average HbA1c level from 9.24% to 6.14% a year after surgery [31].

The "Hindgut" hypothesis tries to explain the metabolic effects of the ileal transposition and states that the improvement in metabolic control is due to an increase in the flow of unabsorbed nutrients in the distal segment of the small intestine. Which leads to the activation of a neuroendocrine negative feedback mechanism often referred to as the "ileal inhibitor." This thesis is proved by the established effects of displacement of the distal segment of the small intestine in the experiment, i.e. the increase in the number and secretory activity of L-cells of the displaced segment of the intestine, increase in the secretion of glucagon-like peptide 1 and -2 (GLP-1, GLP-2), peptide tyrosine-tyrosine (PYY), increase in the mass of β-cells of the pancreas, decrease in their apoptosis and increase in insulin production, and increase in glucose tolerance [38,39,40].

GLP-1 increases glucose-induced insulin secretion, inhibits glucagon secretion, reduces food absorption, improves insulin sensitivity, promotes β-cell regeneration, and reduces their apoptosis, this is how its antidiabetic effect is manifested [41]. PYY, as well as GLP-1, is characterized by stimulation of β-cell regeneration and hypoglycemic effect. Moreover, it participates in the regulation of appetite by reducing it [42].

Another effect of the ileal transposition is to reduce gluconeogenesis and lipogenesis in the liver. In a study by Hung C. et al., the following was observed in rats after the ileal transposition: undigested food passing into the gut lumen triggered the production of chemokines, which reached the liver via the portal vein, therefore, it led to a decrease in the synthesis of glucose and lipogenesis in the body by attenuation of signaling via TGF-β and, consequently, a decrease in the level of hyperglycemia.

The ileal transposition proved to be the most successful metabolic operation in the correction of severe forms of nonobese DM2 in the experiment [43].

In addition, some authors express doubts about the pathophysiological importance of the hypothesis «Hindgut», which is due to the absence of an effect equivalent to metabolic operations in response to antidiabetic drugs stimulating secretion GLP-1 [44]. In contrast to the positive effects of the incretion mechanism and the hypothesis «Hindgut», it is assumed that there are hormonal pathways with adverse effects for glycemic homeostasis, the so-called anti-incretine mechanism, which is launched in response to the passage of nutrients through the proximal sections of the small intestine and the presence of which explains the opposite «Foregut» theory. The anti-incretin effect is expressed in the inhibition of the incretin effect: it causes a decrease in insulin release, a decrease in beta cell proliferation, and inhibition of insulin action to prevent hypoglycemia. [45,46,47].

In this case, it is interesting to study the effects of IT and to develop innovative experimental operational methods, which make it possible to assess changes in the parameters of glycometabolism on DM models with the exception of the anti-incretin mechanism.

The Effectiveness of Bariatric Surgery in DM1.

To date, there is evidence that metabolic operations may improve the condition of patients with DM1 but the data of various authors are contradictory and further research is needed [15,17] in this field.

Initially, it was suggested that the improvement in the condition of patients with DM1 and their increased sensitivity to insulin is due to weight loss after bariatric surgery [48,49]. Currently, the Hussain study (2019) is known, which investigated changes in HBA1c, BMI, and the daily dose of insulin replacement therapy after bariatric interventions in patients with DM1. A decrease in these indicators was revealed but they were statistically unreliable for glycolized hemoglobin. A weak correlation between insulin dose and BMI, as well as a slight correlation between HBA1c and BMI after surgery, was found. According to the author, this dictates the need for further investigation of glucose homeostasis depending on the anatomical changes in the gastrointestinal tract caused by metabolic surgery since each centimeter of the gastrointestinal tract is a complex functional unit, thus, any change affects homeostasis [21].

Nevertheless, A. Chow et al., having conducted a meta-analysis, obtained statistically reliable results. The authors analyzed 13 papers describing the results of Roux-en-Y gastric bypass surgery in 86 patients with obesity and type 1 diabetes mellitus. It was found that their BMI ($p<0.00001$), the need for insulin ($p<0.00001$), and the level of glycolized hemoglobin ($p<0.01$) decreased. However, the target value of HBA1c ≤7.0% was not reached. According to the authors, this was due to an increase in the tolerance of the liver and peripheral tissues to insulin, instead of the effect of GLP-1 on the functions of the endocrine part of the pancreas since patients with DM1 had almost zero functional potential of beta cells [23].

According to Ahn C. H. et al. (2020), the ileal transposition slows the physiological aging of pancreatic β-cells in obese rats, which may contribute to an increase in insulin release following a meal. The mechanism underlying the prevention of the β-cell aging after the ileal transposition may be a new therapeutic target for diabetes mellitus.

It can be concluded that the metabolic effects of the ileal transposition cannot positively affect glycemic control in cases with minimal or zero β-cell functioning in patients with DM1. However, there is an assumption that islet cell regeneration occurs even in patients with long-term DM1. Therefore, the timing of bariatric surgery is crucial since effects mediated by the ileal transposition may contribute to the preservation of β-cell mass [50-52].

Conclusion

Interest in metabolic surgery for diabetes mellitus is growing from year to year. Particularly, when searching for the key expression of "ileal transposition," more than 300 publications are found in the Pubmed (US National Library of Medicine National Institutes of Health) database. The growth trend of publications has an upward exponential dependence.

Modern bariatric procedures, such as RYGB, BPD/DS and transit bipartition, which involve the mechanism of accelerated intake of undigested nutrients to the terminal segments of the small intestine, are the most effective in the correction of morbid obesity and DM. Changes in the anatomy of the gastrointestinal tract during bariatric surgery mediate changes in hormonal regulation that contribute to the remission of diabetes, which requires further study by experimental operations.

Given the absence of an implemented surgical method for the treatment of diabetes mellitus without morbid obesity in clinical practice, the inconsistency and lack of data on the positive metabolic effects of the ileal transposition, it seems appropriate to further study the mechanisms of homeostasis of glucose during experimental operations.

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Validation of the Kazakh-language version of the World Health Organization's WHOQOL-BREF questionnaire on the quality of life among the elderly population of Aktobe city

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Abstract

Introduction: In Kazakhstan, as the phenomenon of population aging becomes more and more relevant, an increasing number of researchers in the field of medicine are studying health-related problems that arise at this age. During these studies, many scientists are wondering: how to accurately measure the quality of life of older people? In our country, the most used tools for conducting this assessment are the SF-36 questionnaire, while the widely used worldwide tools WHOQOL-100 and its short version WHOQOL-BREF are rarely evaluated and used in the Republic of Kazakhstan. Thus, the aim of this study was to determine the psychometric properties of the Kazakh-language version of the World Health Organization's Short Quality of Life Questionnaire (WHOQOL-BREF) in a pilot study.

Material and methods: The WHOQOL-BREF questionnaire was subjected to translation procedures according to the instructions of WHOQOL (WHO) and a pilot study was conducted in a group of elderly respondents (>60 years old) living in the city of Aktobe. The WHOQOL-BREF questionnaire consists of 26 questions, which are divided into 4 areas (physical health, emotional health, social factors, environment). The reliability and validity of the questionnaire was evaluated with the determination of the Alpha-Cronbach's index, as well as the assessment of the intra-class correlation (ICC). The statistical significance was set at 0.05. The software package SPSS v. 10.0 was used for the analysis.

Results: The average age of the participants was 67.3±5.03 years, and the overall WHOQOL-BREF score was 76.02 ±11.86. Overall, 60% of the participants were women. The alpha values for each of the spheres and the overall index (>0.70) and the overall correlation of the elements were satisfactory. The confirmatory analysis of the intra-class correlation showed high ICC values (more than 0.74) for each of the spheres.

Conclusion: The psychometric properties of the Kazakh version of WHOQOL-BREF were acceptable.

Key words: elderly people, cultural adaptation, reliability and validity, quality of life

Introduction

According to the United Nations Population Fund for Demography, Development and Gender (UNFPA), the demographic situation in Kazakhstan is characterized by an increase in the proportion of older people in the age structure of the country's population. At the beginning of 2019, the share of the population aged over 60 years was 11.6% of the total population of the Kazakhstan, and those aged 65 years and older – 7.5% [1]. The country is in the initial stage of demographic aging [2]. At the same time, in half of the country's regions, the 7% threshold characteristic of an aging nation has already been significantly overcome. According to UNFPA projections, the share of older persons aged 65 and over, at 7.3%, will continue to grow by 2050 and will almost double [3]. Although today Kazakhstan is a relatively young nation, it is necessary to think about the trends and consequences generated by the aging of the population in advance.

Older people are more likely to suffer from multiple diseases due to reduced physical and mental functions. Loneliness, sexual dysfunction, and chronic metabolic disorders are some of the causes that can lead to emotional disorders [4]. These problems can reduce the quality of life of older people.

According to WHO, quality of life is defined as a person's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and challenges [5]. In addition, quality of life is described as well-being resulting from a combination of physical, functional, emotional, and social factors [6].

Poor economic, cultural, educational, and health conditions, as well as inadequate social interaction, can lead to a decline in the quality of life of older people [7-9]. Chronic diseases, such as diabetes mellitus, coronary heart disease, osteoporosis and cerebrovascular diseases are the most common diseases in the elderly. These disorders, which cause medical, social and psychological problems, can reduce the physical function and quality of life of older people in society [10-13].

In Kazakhstan, there are not many studies devoted to the study of the quality of life in the elderly population. The few studies conducted in the cities of central significance (Almaty and Nur-Sultan) were conducted mainly using the common SF-36 questionnaire [14], while the WHO questionnaire was not used to study the quality of life. The WHO Quality of Life Questionnaire (WHOQL-100) is one of the most appropriate tools, which is acceptable for use in different cultures and is widely used in various epidemiological studies [15]. The development and testing of the Russian version of the WHOQOL-100 questionnaire was carried out on the basis of the department of psychoprophylaxis and outpatient psychiatry of the St. Petersburg Psychoneurological Institute named after V.M. Behterev, which has the status of a WHO regional research center [16], where it is tested for quality of life. The Russian-language version of the questionnaire is officially recognized by the WHO and is available for general use on the developer's website. The short version of this questionnaire, consisting of 26 questions, has proven its reliability, validity and sensitivity by numerous studies in 19 countries, including Russia. However, there is currently no version available in Kazakh, which is the official language in Kazakhstan. Thus, the aim of this study was to adapt a short version of the WHOQOL questionnaire (WHOQOL-BREF) for use among the Kazakh-speaking population and to assess its reliability and reliability.

Materials and methods

The questionnaires developed for the first time are subject to the mandatory validation procedure, as well as when adapting the already validated questionnaires to the linguistic and cultural characteristics of a particular country. Validation in this case consists of the following stages: translation, preliminary testing, assessment of reliability and, validity assessment. This study was approved by the local bioethical committee at the NJSC "West Kazakhstan Marat Ospanov Medical University". All participants signed an informed written consent prior to the survey.

Our questionnaire validation process consisted of the following stages: Preparation, Translation, Preliminary testing, Assessment of the reliability of the questionnaire

1. Preparation.

Prior to conducting the study using the WHOQOL-BREF questionnaire, an agreement was signed with a group of WHO researchers and appropriate translation instructions were received.

2. Translation.

At 1-st step, the original version of the questionnaire was translated into Kazakh. The translation was carried out by two professional translators, native speakers, independently of each other. The translators were not medical specialists, but certified English language specialists. During the translation process, each of the translators made a direct translation of the original WHOQOL-BREF questionnaire, instructions, and answer options. After comparing both versions of the translation and matching, a combined verified version, Version 1, was created.

At step 2, the verified Version 1 was translated into the original (English) language. The translation was carried out by professional translator, a native English speaker. One of the conditions for the reverse translation was that the translator did not have access to the original version of the questionnaire. These two new versions were compared and served as the basis for a consensus version of the English translation of the questionnaire. This version, Version 2, in the Kazakh language was grammatically and semantically acceptable.

At the 3rd step of creating the Kazakh-language version, a pilot test of the created Version 2 was conducted on patients who were native speakers of the Kazakh language. This step is necessary in order to determine the acceptability of the translation (instructions, questions and answers). After the translation from the original, two main aspects were checked: the equivalence of points and answer options. There were 30 respondents took part in the testing. All the subjects were native speakers of the Kazakh language. The questionnaire was completed by each respondent independently of each other, and if difficulties arose, the subject turned directly to the interviewer. At the end of the survey, the interviewer also asked if the interviewee had any problems, understanding the questionnaire and completing it. During the survey, the wording of the questions and answer options was adjusted based on the wishes of the respondents. There were no changes due to the Version 2 survey. There were 85% of the respondents said that they understood the content and everything is clear from a cultural point of view. Thus, Version 2 of translated questionnaire was accepted as the final version in the Kazakh language.

3. Preliminary testing.

To confirm its applicability in everyday practice, the Kazakh version of the WHOQOL-BREF questionnaire was tested in two stages on 30 native-speaking patients. The criteria for inclusion in the pilot study were:

- elderly age (60–74 years);
- fluency in the Kazakh language;
- absence of concomitant severe somatic or mental illness.

4. Assessment of the reliability of the questionnaire.

Assessment of the reliability of the questionnaire was carried out with the study of such indicators as:

- Internal consistency: Cronbach's Alpha coefficient alpha (α) was used to calculate internal consistency for each area of the WHOQOL-BREF questionnaire. If the values of Cronbach's α coefficient were more than 0.7, then they testified to sufficient internal consistency (Cronbach L. Coefficient alpha and the internal structure of tests. Psychometrica 1951; 16)

- Reliability stability, characterized by the stability of the results over time, was carried out using the test-retest method in a subgroup of 10 participants who completed the questionnaire twice within 10 days. The results of the two tests were compared by calculating the Pearson correlation coefficient. At the same time, a statistically significant correlation coefficient >0.7 testified to the sufficient reliability of the tested questionnaire.

Questionnaire

This WHOQOL-BREF questionnaire is characterized by both brevity and ease of use, as well as multi-dimensionality. It allows you to get an assessment of the quality of life of the respondent as a whole, as well as private assessments for individual domains. It is applicable to a wide range of contingents, covering the full range of functions, disabilities and distresses that relate to quality of life. WHOQOL-BREF is a 26-point questionnaire covering 4 aspects of quality of life (psychological – 6 questions, physical – 7, social – 3, and environmental – 8). The score for each question has answer categories from 1 to 5, with a high score indicating a high quality of life, with the exception of three questions regarding pain and discomfort, the need for treatment, and negative emotions. The physical health measurement includes 7 items (mobility, daily activity, pain, sleep, functional ability, and energy). The psychological field evaluates negative thinking, self-esteem, positive attitude, self-esteem, mindset, learning ability, memory, consolidation, religion, and mental state. Issues such as social support, sexual life, and personal relationships fall within the realm of social relations. The field of environmental health includes questions about financial assets, safety, health and social services, living in a natural environment, learning experiences, relaxation, and the environment such as air, noise, pollution, and transportation [17]. The sum of points in each area demonstrates a person's personal perception of the quality of life. All area scores were scaled positively (a higher score indicates a higher quality of life). The conversion of the raw indicator was done using the WHO developer's spreadsheet given to convert the raw indicator to converted scores. A score above the average (50%) of the total score is classified as an acceptable level of quality of life.

Statistical data processing was performed using the STATISTICA 10 application software package for Windows (StatSoft, USA).

Results

The pilot study involved 30 patients, all of whom were randomly selected from the list of the attached elderly population from Aktobe city. There were no obstacles either in the questions or in the answers section of the questionnaire. One WHOQOL-BREF questionnaire took between 9 and 17 minutes to complete (median = 11 minutes). The socio-demographic characteristics of the respondents who took part in the study are presented in - Table 1.

Table 1 Socio-demographic characteristics of respondents (n=30)

Characteristics	Number of patients	%
Age (year)		
Middle age	67,3±5,03	-
Age ranging	60-74	-
Gender		
Male	12	40
Female	18	60
Education		
Secondary education	3	10
Secondary special education	12	40
Higher education	15	50
Marital status		
Married	21	70
Single	3	10
Widow / widower	6	20

Among the respondents there were 18 women and 12 men. The age of the respondents ranged from 60 to 74 years, while the average age of the patients was 67.3 (±5.03) years. According to the requirements for the translation procedure, all respondents were native speakers of the Kazakh language. As for marital status: 21 (70%) of the respondents were married, 3 (10%) answered "single", 6 (15%) – "widow/widower". 15 (50%) of the respondents had higher education, 12 (40%) – secondary vocational education, and 3 (10%) – secondary education. The survey was conducted by a trained medical professional through a personal interview. To ensure confidentiality, interviews were conducted in a separate room or room separated from other family members or visitors to the clinic.

To assess the reliability of retesting, every 3rd participant was selected from the study, and the same questionnaire was asked to the same member twice, 2 weeks apart.

Reliability

The WHOQOL-BREF questionnaire in Kazakh as a whole and its domain separately had a Cronbach's Alpha coefficient above the boundary value of the indicator $\alpha \geq 0.70$, which indicates an acceptable level of internal consistency of the instrument scales. Thus, the total Cronbach's Alpha index for the Kazakh-language instrument was equal to $\alpha=0,73$. In the questionnaire, the highest value of the coefficient was for the domain of physical health ($\alpha=0,78$), in second place – the domain of psychological health with the indicator $\alpha=0,72$. The lowest value of the coefficient was in the domain of social relations and was equal to the value of $\alpha=0,70$ (Table 2).

As already described in the methods of this study, the assessment of the reliability of the questionnaire in terms of the stability of the results was carried out by re-testing patients and calculating the Pearson correlation coefficient. The time between the initial test and the re-test (t) was an average of 10 days. The values of the Pearson correlation coefficient (r), when studying the reliability of the instrument over time by conducting a re-test, varied from $r=0,70$ to $r=0,78$. This indicator was the lowest for the social relationship domain. The correlation coefficient between the responses of the respondents in the initial and repeated testing for the main questionnaire was $r=0,74$. In each of the 4 domains, the elements are significantly correlated at a level of less than $p<0,05$.

After the pilot study, the next stage of our work was to study the quality of life of the Kazakh-speaking elderly population according to the age-sex characteristics of the city of Aktobe, using the Kazakh-language version of the WHO quality of life questionnaire. In the city of Aktobe, according to the census of 01.01.2020, a population of 500757 people was registered, among them the elderly population from 60 to 74 years old – 42 980 people, of which 16 989 were men, 25 991 were women.

The sample size of 437 older people assigned to the city's primary health care facility was obtained with a 5% margin of error, 95% confidence interval, 50% prevalence, and 20% wastage loss.

56 people refused the study, so the analysis was limited to 381 respondents, while the amount of losses was 12.8%. The multistage cluster sampling method was used and carried out in all polyclinics of the city from November 2019 to March 2020. Guests and temporary residents were excluded from the study. In the city of Aktobe, there are 7 polyclinics that monitor the attached population. In the first step, we randomly selected outpatient clinics using a simple random sampling technique. In the next step, we again selected the number of households in this

Table 2 Internal consistency of the WHOQOL-BREF questionnaire in Kazakh language

Domains	Question No	Average score (SD)	
n=30	Alpha coefficients n=30		
Physical health	3, 4, 10, 15, 16, 17, 18	25.18 (4.26)	0,78
Psychological health	5, 6, 7, 11, 19, 26	22.18 (3.56)	0,72
Social relationships	20, 21, 22	11.64 (1.97)	0.70
Environmental health	8, 9, 12, 13, 14, 23, 24, 25	22.75 (4.73)	0.71
The questionnaire as a whole	1-26	76,02 (11,86)	0.73

Table 3 Time stability of the WHOQOL-BREF questionnaire in Kazakh language

Domains	Question No	Test-retest (n=10)		
		r	p	t
Physical health	3, 4, 10, 15, 16, 17, 18	0,71	0,03	10
Psychological health	5, 6, 7, 11, 19, 26	0,72	0,02	10
Social relationship	20, 21, 22	0,70	0, 005	10
Environmental health	8, 9, 12, 13, 14, 23, 24, 25	0,78	0,01	10
The questionnaire as a whole	1-26	0,74	0,05	10

Table 4 Characteristics of study participants

Characteristic	n (%)
Average age (SD)	66,5 (4,23)
Gender	
Men	182 (47,8%).
Women	199 (52,2)
Marital status	
Married	182 (47,8%)
Divorced	31 (8,1%)
Lonely	12 (3,1%)
Widowed	156 (41,0%)
Education	
Higher	85 (22,3%)
Secondary professional	142 (37,3%)
Primary (school)	154 (40,4%)

selected plot using a random sampling method. In each district, the number of households was proportional to the population in the district.

The survey was conducted by a trained healthcare professional through a personal interview. To ensure confidentiality, interviews were conducted in a separate room or space separated from other family members.

The characteristics of participants in the age range 60-74 years are presented in Table 4.

The average age of 381 elderly people was within 66.5 (4.23) years. Of these, 52.2% - 199 women and 182 men (47.8%). There was no significant difference in the sex ratio in the study (P=0.461). 85 (22.3%) had higher education, 142 (37.3%) had secondary education, and 154 participants (40.4%) had primary education. The family status of the respondents: family (married) amounted to 182 (47.8%), single 12 (3.1%), divorced 31 (8.1%), widowed 156 (41%).

As for the assessment of quality of life indicators (in the range from 1 to 5), the results showed that the overall indicators of the quality of life in participants of both sexes were at an acceptable level and amounted to 85.2 (10.6) and 86.9 (10.3), respectively. The average scores by area and the overall assessment of the quality of life, depending on gender, are shown in Table 5.

As can be seen from the data on the quality of life indicators, there were no significant differences in the general perception of the quality of life among men and women (Table 6). There were no differences in domains in terms of assessing the quality of life in the domains of physical and psychological health, as well as in the domain of social relations. With the exception of the environment and financial resources, where the values of the quality of life in women were statistically significantly higher than in men (p=0.006). It can be assumed that this fact is due to the fact that women at this age feel more mobile and free in movement due to the fact that children have gained independence, there is a stable pension provision, more free time that can be used for their own purposes. Also, children in many cases provide financial support to mothers, which is closely related to the mentality and upbringing in Kazakh society. Whereas men note lower indicators of the quality of life in this area. Perhaps this is due to an increase in the number of chronic diseases and a decrease in income due to retirement, which is one of the key factors in the perception of the quality of life.

As for the assessment of the overall quality of life of the urban elderly population, it was higher than the average and amounted to 85.0 (±10.5) points. The fairly high quality of life among the elderly in the city is possibly due to the limitation of our sample; we did not include elderly patients with severe somatic and psychological illnesses who could not answer the questionnaire in the study. Perhaps people who completed the survey were more satisfied than average with their quality of life.

When assessing the quality of life by age, all respondents were divided according to age into three categories: I - from 60 to 64 years old, II - 65-69 years old, and III from 70-74 years old. Quality of life indicators depending on age are presented in Table 7.

When assessing the quality of life for three age categories, the following data were obtained: higher age was significantly associated with a lower quality of life indicator. When assessing the general indicator of the quality of life, statistically significant differences were revealed between the I and III (5.04, p=0.0000) age categories, between the II and III age categories (2.75, p=0.017), which indicates a deterioration in the quality of life of elderly patients with age.

Table 5 Average value of the quality of life indicator in general and by domains in both sexes

Domains	Elderly people		
	Men n=182	Women n=199	All n=381
1. Physical health			
Daily activities	3.49 (0.81)	3.42(0.83)	3.41(0.83)
Dependence on drugs and excipients	3.10(1.11)	3.02(1.13)	3.05 (1.12)
Energy and fatigue	3.50 (0.92)	3.61 (0.94)	3.57(0.94)
Mobility	3.48(1,01)	3.6 (1.13)	3.55 (1.06)
Pain and discomfort	2.81(1.02)	2.95(1.05)	2.90 (1.05)
Sleep and rest	3.38(1.2)	3.18 (1.20)	3.28 (1.20)
Performance	3.42 (0.84)	3.38(0.87)	3.40(0.86)
Total (7-35)	23.1 (2.61)	23,4(2.51)	23.3 (2.56)
2. Psychological health			
Negative feelings	3.54 (1.30)	3.55(1.18)	3.55 (1.24)
Positive feelings	3.42 (0.83)	3.41 (0.82)	3.42 (0.80)
Self-esteem	3.34 (0.91)	3.52(0.80)	3.44(0.85)
Spirituality / Religion /	3.72 (0.86)	3.58(0.84)	3.66(0.83)
Personal beliefs	3.42 (0.78)	3.34 (0.87)	3.38 (0.82)
Thinking, learning, memory and concentration	3.41(0.92)	3.59 (0.84)	3.51(0.90)
Total (6-30)	22.2 (2.97)	22.3 (2.81)	22,2 (2.89)
3. Social relationships			
Personal relationships	3.96 (0.77)	3.67(0.93)	3.83 (0.87)
Social support	2.98(1.15)	3.02 (1.13)	3.00(1.13)
Sexual activity	3.67 (0.89)	3.32(1.00)	3.50(0.96)
Total (3-15)	10.2 (2.38)	10.0(2.36)	9.87(2.37)
4. Environment Financial resources			
Freedom, physical safety and security	3.44 (0.88)	3.54(0.85)	3.50(0.86)
Healthcare and Social Assistance: Availability and Quality	3.59(0.81)	3.76(0.92)	3.68(0.87)
Financial support	3.25 (1.13)	3.31 (1.14)	3.29 (1.08)
Home environment	3.49 (0.91)	3.53(0.91)	3.51 (0.91)
Opportunities for new information and skills	3.62(0.96)	3.56(0.99)	3.59 (.0.91)
Participation and recreational / leisure opportunities	3.68 (0.90)	3.72(0.89)	3.70(0.90)
Total 8-40	29,5 (4,47)	30,1 (4.57)	30.2 (4.56)
TOTAL by domains	85.2 (10.6)	86.9 (10.3)	85.0(10,5)

Table 6 Comparison of qualitative data by domains of the questionnaire depending on gender

Domains	Men (n=182)	Women (n=199)	*p
Physical health	23.1 (2.61)	23,4(2.51)	0,366
Psychological health	22.2 (2.97)	22.3 (2.81)	0,121
Social relationships	10.2 (2.38)	10.0(2.36)	0,290
Environment and financial resources	29,5 (4,47)	30,1 (4.57)	0,006**
The overall value of quality of life	85.2 (10.6)	86.9 (10.3)	0,119
* p value was calculated using the Mann-Whitney U test			

In the field of physical health, there are statistically significant differences in age categories I and III (4.42, p=0.001), II and III (2.55, p=0.03). Whereas there were no statistically significant differences in age categories I and II (1.91, p=0.16). At the same time, higher age correlated negatively with the area of physical health.

According to the indicators of psychological health and self-perception (domain 2), significant differences were revealed when comparing groups I and II (2.98, p = 0.008), as well as groups I and III (4.18, p=0.000). Significant differences in psychological health between II and III age group was not identified (1.27, p=0.6).

When assessing the indicators of the domain of social relations, statistically significant differences were revealed in indicators of the I and III age groups (3.87, p=0.0003), which indicates a deterioration in the domain of social relations with increasing age.

When assessing the quality of life indicators in domain 4 (environment and financial resources), statistically significant differences were revealed in I and III (4.62, p=0.00001), II and III (3.37, p=0.002) age groups, which also indicates deterioration in the quality of life associated with financial support and the attitude of the environment depending on age.

When assessing the quality of life with and without background diseases, statistically significant differences were observed in the quality of life in respondents with a history of cardiovascular diseases, disorders in the sense organs and comorbid conditions (2 or more diseases in the history) ($p<0.05$). However, these differences were not so obvious in respondents with diseases of the musculoskeletal system and diseases of the gastrointestinal tract. Unambiguously, the presence of one or another chronic disease leads to a significant decrease in the quality of life in all areas, which is confirmed in our study. Respondents with certain chronic diseases had statistically

Table 7 Indicators of quality of life by age

Quality of life metrics by domain	I age group N=135	II age group N=130	III age group N=116	Kruskal - Wallis test	
				r	p
Physical health	23.9 (2.53)		22.56(2.58)	4.42	0.001**
		23.3(2.43)	22.56(2.58)	2.55	0.03*
Psychological health	23.2(2.79)	22.3(2.67)		2.98	0.008**
	23.2(2.79)		21.8(3.06)	4.18	0.000***
Social relationships	10.7 (2.20)	10.0 (2.31)	9.51 (2.47)	3.87	0.000***
Environment and financial resources	31.1 (4.40)		28.7 (4.44)	4,62	0.000***
		30.4 (4.51)	28.7 (4.44)	3.37	0,002**
The overall value of quality of life	89.0(9.89)		82.6(10.73)	5.04	0,000***
		86.2(10.05)	82.6(10.73)	2.75	0.017*

*P<0.05;
**P<0.01;
***P<0.001

Table 8 Relationship between Overall Quality of Life and Disease

Indicators	Average quality of life (SD)	χ2	P
Cardiovascular diseases	81.1 (10.8)	6.96	0.008**
Respiratory diseases	84.5 (10.9)	5.33	0.005**
Diseases of the gastrointestinal tract	83.5 (11.4)	0.10	0.74
Hearing impairment	87.3 (9.97)	6.67	0.001***
Visual impairment	86.0(10.4)	5.14	0.001***
Diseases of the musculoskeletal system	81.4 (11.5)	3.45	0.06
Diseases of the nervous system	88.4 (9.51)	15.06	0.001***

*P<0.05;
**P<0.01;
***P<0.001

Table 9 The relationship between educational attainment and quality of life

Quality of life indicators	Higher education N=85	Secondary education N=142	Primary education N=154	Kruskal — Wallis test	
				r	p
Physical health	24,1(1,99)	22,9 (2,69)		3.05	0.006**
	24,1(1,99)		23,2 (2,64)	2,54	0.03*
Psychological health	23,7 (2,09)	22,0 (3,24)		4,21	0.000**
			22.2 (2,75	4,05	0.000***
Social relationships	10,7 (2,30)	9,89 (2,32)		2,39	0.03*
	10,7		9,98(2,40)	2,24	0,07
Environment and financial resources	32,4 (3,91)	29,3 (4,60)		5,09	0.000***
	32,4 (3,91)		29,7 (4,45)	4,71	0,000***
The overall value of quality of life	91,0 (8.18)	84,1 (11,1)		4,65	0,000***
	91,0 (8.18)		85,2 (10,2)	4,42	0.000***

**P<0.01;
***P<0.001

Table 10 Relationship between marital status and quality of life

Quality of life indicators	Married N=182	Divorced N=31	Lonely N=12	Widowed N=156	P
Physical health	23.4 (2.29)	22.8(1.89)	23.2 (3.62)	23.2 (2,88)	0.6
Psychological health	22.5 (2.65)	22.9 (2.66)	23.0 (4.12)	22,3(3.10)	0.7
Social relationships	10.2 (2.41)	9.77 (2.53)	11.2 (1.86)	9.98 (2.31)	0.32
Environment and financial resources	30.0 (4.23)	30.4 (4.81)	31.6 (6.47)	30.2 (4.73)	0.64
	p value was calculated using the Kruskal-Wallis test *P<0.05; **P<0.01; ***P<0.001				

significantly lower quality of life indicators than patients without diseases. Table 8 depicts the differences between quality of life indicators and comorbidities.

As can be seen from Table 9, the quality of life as a whole was statistically significantly higher among respondents with higher education than among respondents with primary and secondary education. Whereas the quality of life of respondents with primary and secondary education did not differ.

When studying the quality of life depending on marital status (Table 10) we did not reveal statistically significant differences in the quality of life depending on marital status.

Discussion

In the present study, the psychometric properties of the developed Kazakh version of the WHOQOL-BREF questionnaire were tested in a pilot group of elderly patients selected from the total population of the Aktobe city. To avoid selection bias and reduce missing data, we used a personal interview as a survey. The reliability of the WHOQOL-BREF content was analyzed in a pilot group of 30 people (18 women, 12 men, with an average age of 67.3±5.03). The results of the study showed satisfactory alpha coefficients in all areas of WHOQOL-BREF. The Alpha-Cronbach's coefficient was higher than 0,7 on all counts and showed a satisfactory level of internal consistency, which meets the necessary requirements [17]. Differentiation was highest in the physical and psychological domains, followed by the environmental domain, reaching a minimum in the social relationship domain. Compared with the results of the WHOQOL group of Iran [5], Germany [18], Turkey [9], in the Kazakh version, Cronbach's alpha coefficients of social relations were lower. One possible reason may be that after retirement, Kazakh elders are treated as a vulnerable population and are always cared for by their children instead of recruiting them for social activities. The results of other studies showed similar results, indicating the Cronbach's alpha coefficient of less than 0,7 in the field of social relationship [19]. Cronbach's small alpha coefficient in this area was probably also due to the fact that the area of social relations consists of only 3 questions; in addition, interpersonal relationships and sexual activity are relatively different concepts in the culture of the Kazakh-speaking elderly population.

The assessment of the reliability of the questionnaire in terms of the stability of the results over time was carried out by retesting the patients and calculating the Pearson correlation coefficient. The values of the Pearson correlation coefficient (r), when investigating the reliability of the instrument over time by re-testing, varied from r=0,70 to r=0,78, which indicates a high degree of correlation between the responses [20].

Thus, our pilot study showed that the high value of the coefficient of internal constancy (α=0,73) and the reproducibility results of the WHOQOL-BREF questionnaire (r≥0,7) confirm the reliability of its Kazakh-language version. The developed Kazakh-language version of the WHOQOL-BREF questionnaire can be used by domestic scientists and doctors when planning and conducting clinical trials.

The results of the second part of our study showed that the study participants had a high level of quality of life (85.0±10.5). There was no significant difference between the two sexes, however, women had a higher score than men (P=0.119). Moreover, there was a statistically significant difference in the assessment of the quality of life among women in the 4th domain "Environment and financial resources", demonstrating higher indicators than among men (29.5 (4.47) for men and 30.1 (4.57) for women, p=0.006). Most likely, this fact is due to the fact that women at this age feel more mobile and free to move. Perhaps this is due to the fact that children have gained independence, there is a stable pension provision, a greater amount of free time that can be used for their own purposes. Also, children in many cases provide financial support to mothers, which is closely related to the mentality and upbringing in Kazakh society. Whereas men note lower indicators of the quality of life in this area. It can be assumed that this is most often associated with an increase in the number of chronic diseases and a decrease in the level of income in connection with retirement.

With regard to the effect of gender on quality of life, several studies have produced very different results. For example, in a study of domestic scientists who studied the quality of life of 236 elderly and senile respondents in the city of Nur-Sultan using the widespread questionnaire SF-36, men noted a higher standard of living [14]. At the same time, scientists noted that women have a more pronounced significant restriction of physical activity even when lifting a bag with food - 25.3% of elderly respondents and 34.8% of elderly respondents have significant restrictions. Accordingly, these same indicators are 13.8% and 27.8% among male respondents. A decrease in the stability of vitality in women was indicated by the fact that 20% of women were often very nervous, 27.2% of women often felt tired. For men, these numbers are 11.8% and 24.2%, respectively. The opposite criterion, such as role functioning, the intensity of pain is noticeably higher in women than in men.

In a study by scientists from Iran, Yaser et al. who studied the quality of life and related factors of 184 elderly people living in Tabriz (Iran) did not reveal a significant difference in the indicators of the quality of life among men and women (p=0.43), and there were no statistically significant differences separately by spheres. At the same time, the average indicators of the quality of life corresponded to an acceptable level [21]. Agreeing with this result, Ahmadi et al. [22] showed that there were no significant differences between sex and quality of life among 200 elderly people in the city of Zahedan aged 65 and over, according to the SF-36 quality of life questionnaire. It can be assumed that this is due to cultural beliefs and gender discrimination in the countries of the Muslim world. However, these findings have not been supported by studies conducted in Europe, where gender equality is one of the key criteria for the development of society.

In our study of the impact of education and marital status on quality of life, we found mixed results. When studying marital status, we did not reveal statistically significant differences both in individual areas and in the overall perception of the quality of life of the respondents, although in absolute terms the standard of living among single and unmarried individuals was slightly lower. While assessing the level of education and quality of life, it was found that the higher the level of education, the better the quality of life, which was confirmed by statistical data processing. Our data correlate with the results of similar studies in China. When studying the quality of life of the urban population in China in 1,052 adult respondents, of whom 192 (18.3%) were over the age of 60 [23], the results showed that men had a significantly higher level of quality of life in the psychological field than women (p=0.05). While marital status is not related to quality of life, socioeconomic status, as measured by education and income, is largely related. Further analysis showed that, after controlling for other relevant variables, education has significantly more positive effects than income. Participants with a higher level of education had significantly

higher physical, psychological, social and environmental factors of quality of life than those less educated. Inhabitants without chronic diseases, the physical quality of life was significantly higher than in residents with chronic diseases. In addition, employed persons have a significantly higher physical and social level of quality of life than unemployed persons.

In studies in Norway, which studied a random sample of the Norwegian population (n=654) aged 18-75 years using the WHOQOL-BREF questionnaire, 226 participants (36%) of them elderly did not reveal statistically significant differences in the quality of life among the population by gender [24]. In a random sample of 1492 Dutch people aged 50 and over, [25] conducted a study to compare the relationship of gender, age, marital status, education and income with quality of life assessed by different questionnaires SF-12, WHOQOL-BREF and WHOQOL-OLD.

Higher age was associated with lower quality of life in 6 of the 12 quality of life domains. Being married or cohabitating, having a college degree, and having a higher income were associated with higher scores in 11, 10, and all 12 quality of life domains, respectively. However, the meaning of the influence of gender is completely different. In six areas of quality of life, women experienced significantly lower quality of life. Conversely, they experienced significantly better quality of life in three areas, all of which belong to the WHOQOL-OLD (sensory ability, autonomy and social participation). This questionnaire is more specific for conducting research on the quality of life among older people, which is a direction for further research in this area.

Younger age is associated with lower quality of life in rural areas of southern Brazil [26]. Brazilian people in the 60 to 69 age group rated their quality of life, as assessed by the WHOQOL-BREF, lower in psychological and social relationships and overall quality of life. than people over 80. Soósová [27] showed that life without a partner is negatively associated with quality of life. On the other hand, using the same tool, Gobbens RJJ, van Assen M [28] demonstrated that marital status (married or living together) is associated only with the quality of intimacy in the domain of life, after controlling for other sociodemographic factors (age, education, and income).

More years of education were associated with higher scores in psychological, social relationships and environmental quality of life [29]. Additionally, in a study by Gobbens et al [30] higher education institutions are only significantly associated with improving the psychological and environmental quality of life. Soósová [27] observed a higher quality of life among older people with higher education.

However, this study had some limitations. The main limitation of this study was the small sample size of participants. In addition, we did not examine all the psychometric properties of the Kazakh-language version of the WHO questionnaire. Despite the assessment of some of the related factors affecting quality of life, the study of other factors was not possible in this study and may be proposed for future research.

Conclusion

This study demonstrates the good reliability and validity of the Kazakh language version of WHOQOL-BREF. Combined with the general scale, it can be used to contruct an evaluation system for measuring quality of life among older people.

This research is carried out only in the city of Aktobe. We then want to increase the sample size and conduct a multicenter study in Kazakhstan to assess its overall psychometric characteristics.

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Analysis of Publications on Acinetobacter: A Scopus Database Search Study

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Abstract

Aim: We aimed to review the global literature on *Acinetobacter*, which is a global health problem, and identify and characterize the publications to direct scientific studies.

Material and methods: We conducted a bibliometric analysis by searching the Elsevier' Scopus database. This database is one of the biggest international bibliometric database. We searched original research articles from this database using the keywords *"Acinetobacter"* or *"Acinetobacter spp."* and "Article" since July 05, 2021. We carried out detailed analysis to identify the characteristics of articles by using the bibliometric data analysis technique. The articles were analyzed due to the following characteristics: the country of origin, authors' names and affiliations, year of publication, content, number of citations and impact factor.

Results: The total number of publication on *Acinetobacter* were 35587 and the first publication was published in the year 1974. 30074 of these studies were research articles. Only research articles were evaluated in our study. There was a rapid increase in the number of articles after the year 2000 and the number of articles did not decrease until 2020 over the years. There was a decrease in the number of published articles in the year 2020. The majority of the articles (n=26862, 89.31%) were written in the English language. Chinese was the second most preferred language. The most scientifically productive countries on *Acinetobacter* literature were the United States, China and India. Ronald N Jones (n=174) from the USA and Harald Seifert (n=114) from Germany were the most productive authors on *Acinetobacter* research.

Conclusion: As a result, both the number of articles on *Acinetobacter* and the number of citations were quite high. Since the *Acinetobacter* genus is one of the most important pathogens in hospital infections, it seems that researchers will continue to work on this topic.

Key words: *Acinetobacter*, bibliometric analysis, Scopus

Introduction

Acinetobacter genus is Gram-negative, double or chained cocci or coccobacilli, non-spore-forming, sometimes encapsulated, aerobic, oxidase-negative, catalase-positive bacteria [1,2]. There are difficulties in treatment, especially because they have multiple antibiotic resistance and cause hospital infections, especially in intensive care units, globally. It has been shown that there are 12 different genomic types in its taxonomic classification. There are 49 species in the genus *Acinetobacter*. The clinically important species are A. calcoaceticus- *A. baumannii* (genomic strain 2), *Acinetobacter* nosocomial (genomic strain 13TU), *Acinetobacter* pittii (genomic strain 3), and *A. calcoaceticus* (genomic strain 1), which are clinically important species [2,3]. *A.baumannii* complex (ABC) cannot be distinguished biochemically. *Acinetobacter* spp. is the most common cause especially in hospital-acquired pneumonia and bloodstream infections and their antibiotic resistances rates increase over the years (41%, 36%) [1-5].

Although *Acinetobacter* species are generally considered as pathogens with low virulence, that group bacteria have multiple virulence factors. It emerges as

an opportunistic pathogen that causes nosocomial infections with severe clinical manifestations, especially in patients with underlying disease and various risk factors [6]. Factors such as prolonged use of antibiotics, prolonged hospitalization in the hospital and especially in the intensive care unit, long-term use of medical equipment such as catheters and implants, being connected to a ventilator, cardio-pulmonary disease, extensive burns, change in consciousness and immune system deficiencies are related attributable risk factors for *Acinetobacter* infections development. Among *Acinetobacter* species, *A. baumannii* are known as the most virulent species. Multivariate analyzes revealed that the mortality of *A. baumannii* infections is nine times higher than infections caused by other species [6,7]. *A. baumannii* is at the top of the list of 'resistant bacteria that urgently require new antibiotic discovery' due to the increasing resistance rates published by the World Health Organization in the year 2018 [8]. Due to the antimicrobial resistance problem, studies to elucidate the virulence factors and antibiotic resistance mechanisms of *A. baumannii* should continue without slowing down in order to treat *Acinetobacter* infections. It should not be forgotten that researches on the inhibition of virulence factors with different methods, especially molecular methods, new applications that can be an alternative to antibiotic treatment, researches to be carried out for the development of efflux pump inhibitors and antibiofilm agents are very valuable in terms of the control of infections and public health worldwide [9].

We aimed to review the world literature on *Acinetobacter*, which is a global health problem, and identify and characterize the publications to direct scientific studies. To our knowledge, our study is the first bibliometric research in the field of *Acinetobacter* by using the Scopus database.

Material and methods

Research model

In this study, bibliometric analysis method was used as a research model, which is one of the qualitative research method [10]. With this method, studies on a subject can be analyzed mathematically on the axis of various research parameters, including publication years, general characteristics, authors and institutions, keywords, funding institutions, citations, methods and samples [10].

The data of the study were obtained using the Elsevier Scopus bibliometric database, which is one of the main the international databases. This database, providing access to articles and references contained in these articles, allows it to search both forward and backward in time [10]. We searched original research articles from this database using the keywords "*Acinetobacter*" or "*Acinetobacter spp.*" and "Article" since July 05, 2021. Duplications were included in the study only once. The obtained data were analyzed in the Excel file created by the researcher.

Çanakkale Onsekiz Mart University's online library and digital resources were used to access information.

Data analysis

We carried out detailed analysis to identify the characteristics of articles by using the bibliometric data analysis technique. The articles were analyzed due to the following characteristics: the country of origin, authors' names and affiliations, year of publication, content, number of citations and impact factor. Also statistical analyzes (frequency and percentage) were performed to analyse the publications by using Statistical Package for the Social Sciences (SPSS) for Windows Version 23.0 software (SPSS Inc., Chicago, IL, USA). Data were reported as mean ± standard deviation values, number and percentage. Descriptive statistics were used in the statistical evaluation.

Ethics committee

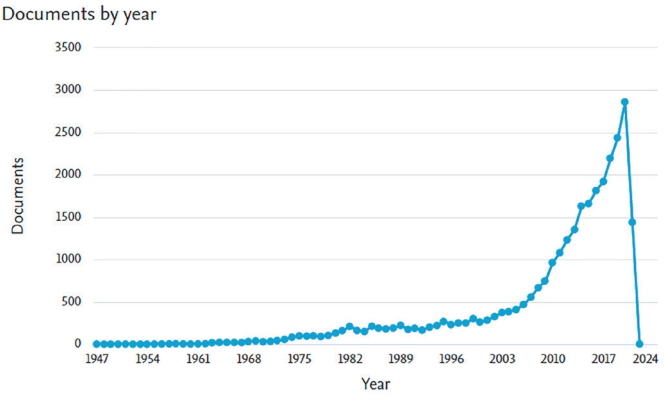
The study complied with the Helsinki Declaration, which was revised in 2013. Ethics committee approval is not required as there is no human or animal research.

Results

It was determined that there were 35587 publications on *Acinetobacter* topic and the first publication was published in the year 1974. 30074 of these studies were research articles. Only research articles were included to our study.

The greatest number of articles published in the last 20 years period from 2000 to 2020 and the number of articles did not decrease since 2020. In 2020, there was a decrease in the number of published articles (Figure 1).

Figure 1 - Number of published articles by years.



The most scientifically productive countries on *Acinetobacter* literature were the United States (USA), China and India. Turkey was in 9th place. The countrywide contribution of the articles is shown in Table 1.

Table 1 The countrywide contribution of the articles (n=30074).

Country	Number of publications	Percentage by total number of publications
USA	5049	16.78
China	4559	15.15
India	2218	7.37
United Kingdom	1529	5.08
Germany	1410	4.68
France	1306	4.34
Japan	1236	4.10
Spain	1060	3.52
Turkey	1034	3.43
South Korea	985	3.27

The majority of the articles (n=26862, 89.31%) were written in English language. Chinese was the second most preferred language. 12503 (41.57%) of the articles were published in open access (AE) (Open Access) journals. Ranking of institutions according to the number of contributions to research given in Table 2. The institution with the highest number of contributors is Ministry of Education China (n=363). China-based institutions were in the first two places among the institutions with the highest number of publications.

Table 2 The list of top 15 institutions contributing the Acinetobacter literature (n=30074).

Institution	n	%
Ministry of Education China	363	1.20
Chinese Academy of Sciences	283	0.94
Inserm	179	0.59
Zhejiang University	178	0.59
Tel Aviv University	177	0.58
Mahidol University	175	0.58
Hospital Clinic Barcelona	175	0.58
Universidade de Sao Paulo - USP	168	0.55
National Taiwan University Hospital	168	0.55
CNRS Centre National de la Recherche Scientifique	165	0.54
Monash University	159	0.52
Tehran University of Medical Sciences	151	0.50
Russian Academy of Sciences	150	0.49
National Yang-Ming University Taiwan	145	0.48
The University of Queensland	141	0.46

Table 3 The List of Top 10 Journals Contributing the Acinetobacter Literature (n=30074).

Journals	n	%	CiteScore 2020	SCImago Journal Rank
Antimicrobial Agents And Chemotherapy	874	2.90	9.1	2.070
Journal of Antimicrobial Chemotherapy	541	1.79	9.1	2.124
Plos One	465	1.54	5.3	0.990
Frontiers In Microbiology	400	1.33	7.3	1.701
Journal of Clinical Microbiology	396	1.31	9.4	2.349
International Journal of Antimicrobial Agents	323	1.07	12	1.454
Diagnostic Microbiology And Infectious Disease	306	1.01	4.6	1.027
Chemotherapy	282	0.93	3.7	0.539
American Journal Of Infection Control	279	0.92	4.2	1.004
Chinese Journal Of Infection And Chemotherapy	278	0.92	0.4	0.112

* SCImago Journal Rank: SCImago Journal Rank measures weighted citations received by the serial. Citation weighting depends on subject field and prestige (SJR) of the citing serial.

Figure 2 - Number publications according to journals contributing the most to the related literature on Acinetobacter.

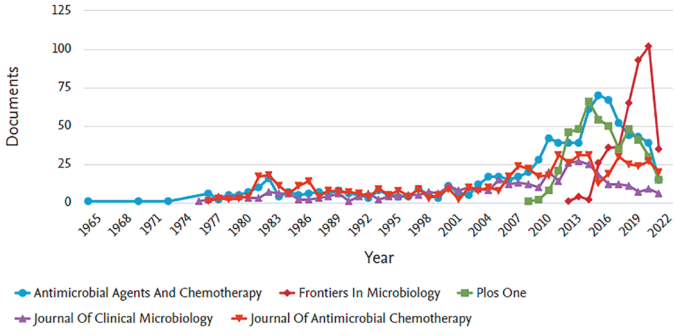


Figure 3 - Documents by authors.

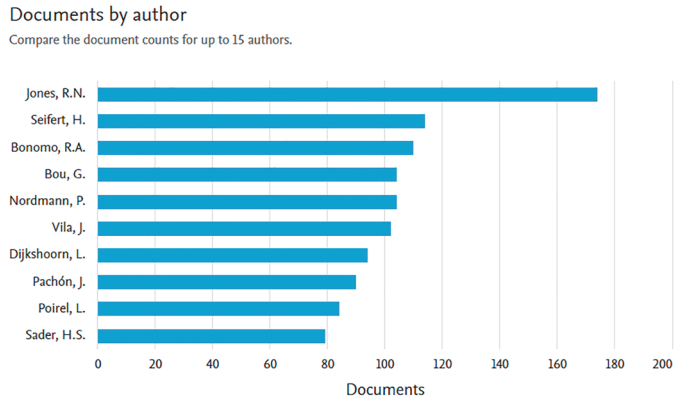


Table 4 The List of Most Cited Publications on Acinetobacter.

Author, Year	Document title	Source	Cited by
Magiorakos,2012	Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance	Clinical Microbiology and Infection	4988
Boucher,2009	Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America	Clinical Infectious Diseases	3277
Wisplinghoff,2004	Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study	Clinical Infectious Diseases	3111
Ventola,2015	The antibiotic resistance crisis: Part 1: causes and threats	P and T	1990
Vincent,2009	International study of the prevalence and outcomes of infection in intensive care units	JAMA - Journal of the American Medical Association	1968
Gao,2013	Human infection with a novel avian-origin	New England Journal of Medicine	1776
Zhang,2015	Comprehensive evaluation of antibiotics emission and fate in the river basins of China: Source analysis, multimedia modeling, and linkage to bacterial resistance	Environmental Science and Technology	1649
Hammer,1999	Antimicrobial activity of essential oils and other plant extracts	Journal of Applied Microbiology	1636
Hidron,2008	Antimicrobial-resistant pathogens associated with healthcare-associated infections: Annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007	Infection Control and Hospital Epidemiology	1525
Tacconelli,2018	Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis	The Lancet Infectious Diseases	1177

The list of the top 10 journals according to the number of publications on *Acinetobacter* given in Table 3 and Figure 2. The journal with the highest number of articles on *Acinetobacter* is Antimicrobial Agents and Chemotherapy (n=874).

Documents by authors are given in Figure 3. Ronald N Jones (n=174) from USA and Harald Seifert (n=114) from Germany were most productive authors on *Acinetobacter* releated publications (Figure 3).

Twelve of the articles were cited more than 1000 times, 38 of them more than 500 times, 155 of them more than 250 times, 1034 of them more than 100 times, among all the articles on *Acinetobacter*. The article written by Magiorakos was the most cited article (n=4988) on *Acinetobacter*

Discussion

Bibliometric analysis which is social science study area, has been started to use in medical area in recent years. As different researchers made this analysis on different medical topics, it became easier to give way to perspective for future studies [11-16]. Pubmed, The Web of Science (WOS) and Scopus databases are mostly common databases mainly preferred in bibliometric analyses [11-16]. *As Acinetobacter* infections are common nosocomial pathogens all over the world and WHO reported it as an emerging pathogen we choose *Acinetobacter* keyword to highlight the importance of this topic and sought to give a bibliometric overview of the literature on *Acinetobacter*, by using Scopus database, which was used in previously published bibliometric studies. As a result of our study we detected the greatest number of articles published in the last 20 years period from 2000 to 2020. But there was a rapid decrease in the number of articles by the year 2020. This status may be relevant to the pandemic.

In only similar study from Turkey on *Acinetobacter* topic. In this study, scientific publications on *Acinetobacter bacteremia* were analyzed by using the Web of Science (WOS) database. This study was limited to *Acinetobacter* bacteremia [11]. Our study had wider range on *Acinetobacter*. And similarly to our study, number of publications on *Acinetobacter* topic have been increasing and growing rapidly in the past decade. In this study the first article was written in the year 1985 [11]. In our study first article was written in the year 1965. The reason for this can be interpreted as the concept of *Acinetobacter* may have been understood after about 20 years to cause bacteremia.

In a study from Iran, a bibliometric analysis was conducted with using WOS database and co-citation analysis was made with the "TI" tag using Ravar PreMap, UCINET 6.528.0.0, and Netdraw 1.0.0.0 programs [12]. "Seifert, Harald" from Germany was found as the most productive author on *Acinetobacter* topic. In our study Ronald N Jones (n=174) from USA and Harald Seifert (n=114) from Germany were the authors with most publications on *Acinetobacter*. The reason for the difference may be the narrower distribution of the WOS database. Magiorakos et al was the most cited author in our study. But in Danesh et al.'s [12] study "Seifert, Harald * Higgins, Paul G" were the top cited authors. This was attributed to the fact that we did not use a similar database with our study.

When the studies on *Acinetobacter* are examined in terms of the publication language, it is seen that the English is the mostly preferred language [11,12]. Our study findings were similar. The majority of the articles (n=26862, 89.31%) were written in English language. Chinese was the second mostly preferred language. This situation shows that English is dominant in the literature. This finding shows that *Acinetobacter* topic has globally importance.

As mostly previously studies [11-17], our study showed that the majority of articles from USA. This may due to research findings and large number of researchers in USA. But the top cited article was published by authors from European Centre for Disease Prevention and Control team [18]. This may be due to the fact that there is a reputable scientific community in the area of Infectious Diseases. In addition, the most cited 3 articles were published in the Clinical Microbiology and Infection journal, and this may due to the fact that this journal with a high impact factor and it is one of the most respected journals in the area of Infectious Diseases.

As a result, both the number of articles on *Acinetobacter* and the number of citations are quite high. Since *Acinetobacter* genus is one of the most important pathogens in hospital infections, it seems that researchers will continue to work on this subject.

Limitations of the study

In this study single database used for research. So, we cannot say that the findings obtained in the research we conducted in a single database represent the total literature on *Acinetobacter*. As bibliometric databases only indexes the academic publications that it covers. International citation indexes include only academic publications indexed in the used database. So regional literature which don't listed in international citation indexes don't have international visibility. This is the second limitation of our study.

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Effects of E407a on the viability, metabolic and functional activity of dermal fibroblasts

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Abstract

Aim: To evaluate the effects of semi-refined carrageenan (E407a) on the viability, metabolic and functional activity of skin fibroblasts in vitro.

Material and methods: Various concentrations of E407a (0 – 10 mg/ml) were incubated for 24 h with skin fibroblast cultures isolated from rat embryos. The viability of cells exposed to semi-refined carrageenan was assessed by the neutral red uptake assay. MTT test was selected to estimate the metabolic activity of cells. In addition, scratch assay was used to determine the functional activity of dermal fibroblasts.

Results: Direct exposure to semi-refined carrageenan did not affect the viability of rat dermal fibroblasts, evidenced by the results of MTT and neutral red uptake assays. However, experimental data of MTT and scratch assays revealed that high concentrations of this food additive increased the metabolic activity of fibroblasts and diminished the motility of these cells, suggesting that E407a is cytotoxic at high concentrations.

Conclusion: Food-grade semi-refined carrageenan is cytotoxic towards skin fibroblasts at high concentrations.

Key words: neutral red uptake assay, MTT assay, scratch assay, carrageenan

Introduction

Food additives are either naturally occurring or artificial compounds whose purpose is to improve the texture of foods, increase their shelf-life and improve their organoleptic properties. International regulatory authorities such as the U.S.-based Food and Drug Administration (FDA) and European Food Safety Authority (EFSA) have initiated the thoughtful re-evaluation of food additives to guarantee their safety for consumers. Among the food additives whose safety is debated, carrageenans seem to be the most controversial [1-5]. Carrageenans are phycocolloids of heteropolysaccharide origin commercially produced from red algae and widely represented in human diet. Cost-effectiveness and convenience of their application in technological processes make them indispensable in the production of processed and ultraprocessed food. The content of carrageenans, which are registered as native carrageenan (E407) and semi-refined form (E407a) can vary to a high extent and may reach 0.5-1% of weight for some dairy products, processed meat and fruit-based processed foods [5].

Carrageenans are flexible molecules with the helical structure extracted primarily from red algae of the genus *Eucheuma* and composed of alternating 1,3-linked D-galactopyranosyl and 1,4-linked D-galactopyranosyl units [6]. There are three basic forms of carrageenan: kappa, iota, and lambda, which differ in their structural properties, sulfation degree, and technological characteristics in the food industry. Nowadays all major forms of carrageenans are recognized as safe for consumption by humans. However, their safety has been challenged by multiple experimental animal studies, culture-based experiments and even some clinical trials [1, 7-13]. Of note, several mechanisms have been suggested to be implicated in carrageenan-mediated gut toxicity. For instance, carrageenan has been shown to inhibit gastric and intestinal proteases such as pepsin and trypsin, reducing in this manner dietary protein bioavailability [5]. Moreover, this food additive has been demonstrated to increase the intestinal permeability, compromising the barrier function [5]. This becomes critical in case of the compromised mucus layer, which can cause direct exposure of intestinal lining to carrageenans.

Furthermore, several recently published papers emphasize the ability of carrageenans to aggravate intestinal inflammation by modulating the gut microbiota [14-16]. Carrageenans have been reported to impair glucose metabolism, contributing to insulin resistance [17, 18]. Despite numerous and diverse data on the effects of orally ingested carrageenans, cell cultures provide controversial conclusions concerning the safety profile of E407a [1, 8, 19, 20]. This suggests that more cell culture-based experiments are required to analyze the impact of carrageenans on cells. In particular, scarce information on the effects of carrageenans on fibroblasts is available.

The aim of this research was to analyze the impact of E407a on the viability, metabolic activity and motility of skin fibroblasts to assess its cytotoxicity.

Material and methods

Fibroblast cultures

Fibroblasts were isolated from skin of rat embryos using the enzymatic tissue dissociation procedure [21]. Briefly, skin was separated, fragmented and incubated with 0.25 % trypsin-EDTA (BioWest, France) during 1 h at 37ºC using a magnetic stirrer. Thereafter, trypsin was inactivated by 10% fetal bovine serum (FBS, Lonza, Germany) via cell filters with a 100 µm pore size. Cells were washed in DMEM (BioWest, France) enriched with 10% FBS. The fibroblasts were seeded in 25 cm2 culture flasks (SPL, Republic of Korea). As soon as the 100% confluence was achieved, the fibroblasts were harvested using 0.25 % trypsin-EDTA and passaged at a ratio of 1:2. The cells were used at passages 3-4.

The European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (EST 123), Directive 2010/63/EU for the Protection of Animals Used for Scientific Purposes, and Recommendation 2007/526/EC were followed. The study was approved by the Commission on Ethics and Bioethics (Kharkiv National Medical University, Kharkiv, Ukraine; minutes #5 d.d. September 17, 2019).

Neutral red uptake assay

The neutral red uptake assay was used to evaluate the viability of cells exposed to the food additive E407a [22]. The fibroblasts were seeded in 96-well plates (SPL, Republic of Korea). The amount of cells per well was 1×104. We used the concentrations of E407a, as well as negative and positive controls, similar to those described above. After incubation of samples for 24 h in a CO_2-incubator (5% CO_2), 0.1 ml culture medium was incubated with a neutral red dye at a final concentration of 0.003% during 3 h in a CO_2-incubator (5% CO_2). Then the medium was collected and 0.1 ml of 50% ethanol and 3% acetic acid were added to extract and dissolve the neutral red dye. Absorbance was determined at 570 nm. Numerical values are expressed in optical density (OD) units.

MTT assay

To analyze the metabolic activity of cells treated with E407a, fibroblasts were seeded into 96-well plates (SPL, Republic of Korea) at a concentration of 1×104 per well. The experiment was performed the next day after seeding, adhesion and formation of fibroblast monolayers.

The cells were incubated with E407a for 24 h in a CO_2-incubator (Thermo Fisher Scientific, USA) at the concentrations of 10, 25, 50, 100, 200, 500, 1000, 5000, 10000 µg/ml (n=8 in each group of samples, 37ºC, 5% CO_2). The negative and positive controls included the cells incubated with no carrageenan and fibroblasts killed by 70% ethanol, respectively. Then the medium was discarded and 0.1 ml culture medium with 15 µl MTT at a concentration of 5 mg/ml was added. Incubation in a CO^2-incubator lasted for 3 h at 37ºC and 5% CO_2. Thereafter, the medium was collected and 0.1 ml dimethyl sulfoxide with sodium dodecyl sulfate was added to dissolve formazan. This was followed by incubation for 1 h at 37ºC. Absorbance was measured at 570 nm. Numerical values are expressed in optical density (OD) units.

Scratch assay

To assess the alterations of mobility and proliferation under the influence of E407a, the scratch assay was carried out [23]. The next day after seeding fibroblasts in 24-well plates at a concentration of 1×10^5 per well, a dispensable pipette was used to make a scratch in a 100% confluent cell monolayer. The cells were incubated with E407a using the concentrations and conditions outlined above. The width of the damaged area was measured directly after making the defect, as well as after 24 and 48 h, respectively. The width of cell-free areas was determined in three regions (top, middle, and bottom) of each well.

To visualize data, a Delta Optical NIB 100 inverted microscope (Poland) and Sigeta MCMOS 3100 3.1MP camera (China) were used. Images were processed using ToupView V 3.7 software (Hangzhou Toup Tek Photonics Co. Ltd, Hangzhou, China).

Statistical analysis

The distribution normality was assessed by the Shapiro-Wilk test. The non-parametric Kruskal-Wallis followed by the Dunn's test was used to detect the statistically significant differences between several independent groups of variables. Data are demonstrated as the median (Me) and interquartile range (IQR; 25%–75%). A value of p below 0.05 indicated the statistically significant difference. Graph Pad Prism 5.0 application was used to perform the statistical analyses.

Results

Visually, no noticeable changes in the fibroblast monolayers were observed compared with the control samples if smaller concentrations of E407a, i.e. below 5 mg per ml, were used. The cells were characterized by a prolonged shape. They were tightly attached to each other. The monolayer was 100% confluent. When higher concentrations were applied, i.e. 5 mg/ml and over, the fibroblasts partially lost adhesive properties, became polygonal and the confluence was approximately 40-50%. However, the complete loss of adhesion was not detected (Figure 1). It is worth noting that the changes were reversible. The next day after the removal of E407a, the monolayer structure returned.

Figure 1 - Cultured fibroblast monolayers treated with various concentrations of the food additive E407a (A - 0 µg/ml; B - 100 µg/ml; C - 5 mg/ml) during 24 h. Phase contrast microscopy. The scale bar is 100 µm.

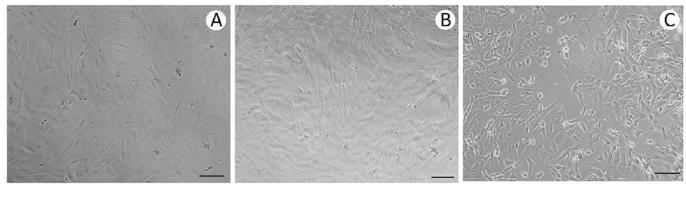


Figure 2 - Representative images of cultured dermal fibroblasts exposed to different concentrations of the food additive E407a (A - 0 μg/ml; B - 100 μg/ml; C - 5 mg/ml) for 24 h and subsequently stained with the neutral red dye. Phase contrast microscopy. The scale bar is 100 μm.

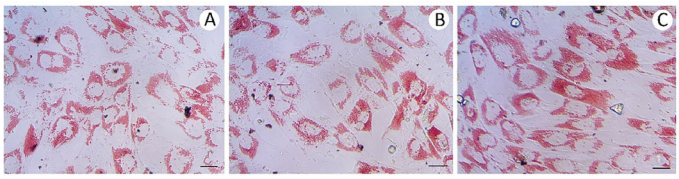


Figure 3 - The viability of fibroblasts exposed to E407a at concentrations 0-10 mg/ml for 24 h was assessed by neutral red uptake assay. Numerical data are presented in optical density (OD) units. The food additive E407a was not found to affect cell viability.

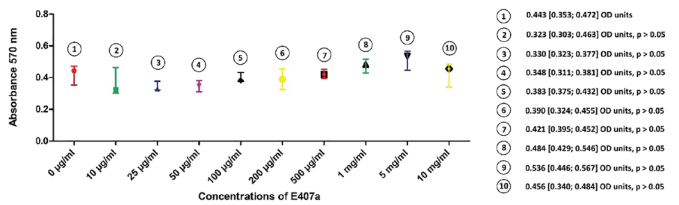
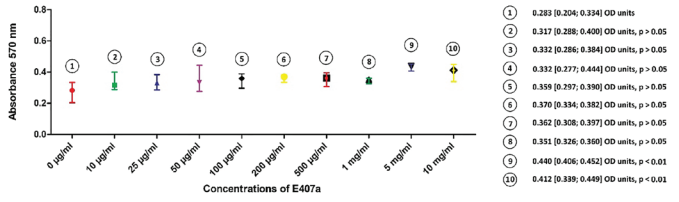


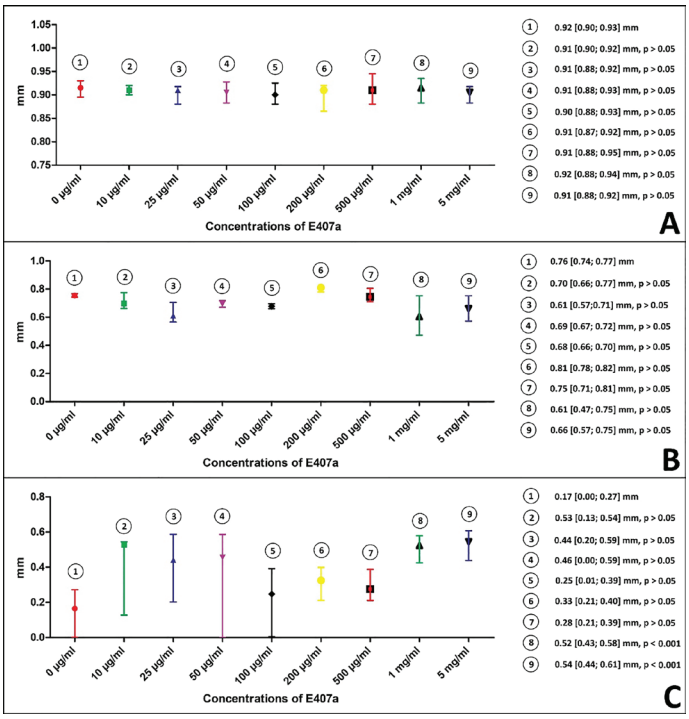
Figure 4 - The metabolic activity of dermal fibroblasts treated with semi-refined carrageenan (E407a) for 24a (0-10 mg/ml of the food additive) was estimated quantitatively using MTT assay. Numerical values are expressed in optical density (OD) units. Exposure to E407a at a concentration of 5 mg/ml and higher statistically significantly increased the metabolic activity of fibroblasts compared with control samples.



A complex evaluation of E407a cytotoxicity towards rat skin fibroblasts was performed. Data of MTT test and neutral red uptake assay showed that carrageenan had no effect on cell viability, which was confirmed by the absence of statistically significant ($p>0.05$) reduction of optical density values in fibroblast suspensions treated with carrageenan and subsequently stained with vital dyes: MTT and neutral red (Figures 2-4). On the contrary, the statistically significant ($p<0.01$) elevation of optical density values in samples incubated with 5 mg/ml and 10 mg/ml of E407a for 24 h while carrying out the MTT assay suggested that E407a increased the metabolic activity of cells. The increase in the parameter studied was 1.6- and 1.5-fold, respectively (Figure 4).

The same trend was observed in case of the functional scratch assay. Concentrations of semi-refined carrageenan below 1 mg/ml did not have any impact on the motility of fibroblasts, evidenced by no statistically significant changes ($p>0.05$) in the width of cell-uncovered regions within 48 h after the assay performance (Figure 5). However, after 48 h almost a 3-fold reduction in the size of cell-free areas was revealed in the samples exposed to high concentrations of E407a (over 1 mg/ml).

Figure 5 - Scratch assay was used to assess the motility of fibroblasts after exposure to semi-refined carrageenan (E407a) for 24a at the concentrations of 0-10 mg/ml. The width of cell-free areas was compared followed a formation of scratches by a pipette time after 0, 24 and 48 h, respectively. Semi-refined carrageenan at concentrations of 1 mg/ml and above statistically significantly reduced the motility of fibroblasts compared with controls.



Discussion

The complex assessment of semi-refined carrageenan cytotoxicity to skin fibroblasts performed in this study shows that partial toxic effects are typical only for high concentrations of this food additive. Our experimental data prove that the concentrations exceeding 5 mg/ml increase the metabolic activity of cells against the background of the reduction of functional activity, i.e. motility of fibroblasts. A higher metabolic activity of fibroblasts induced by exposure to high concentrations of E407a may indicate the compensatory mitochondrial hyperactivation as a part of the stress-induced response. Since MTT is converted to formazan in mitochondria, our findings suggest that the carrageenan toxicity is at least partially associated with mitochondria-mediated mechanisms. There is some evidence that such changes in the results of MTT viability assays may be due to either mitochondrial biogenesis, which can compensate for the damage to mitochondria caused by E407a, or even a higher generation of formazan by the reduced number of overactivated surviving cells [24].

Our data are consistent with other findings, in particular, the inability of different types of undegraded carrageenan to promote cell death in human intestinal and hepatic cells [19, 20]. Degraded carrageenan, whose toxicity is compellingly demonstrated, induced apoptosis and blocked cell proliferation in normal and cancer intestinal and hepatic cell lines [19].

It is important to mention that immune cells are more sensitive to carrageenan cytotoxic effects. Our earlier studies demonstrate the uptake of semi-refined carrageenan by leukocytes and anti-apoptotic bcl-2 upregulation in lymphocytes in vitro, as well as excessive ROS production and activated apoptosis of circulating leukocytes after E407a ingestion in

vivo [25, 26]. Moreover, semi-refined carrageenan increases the metabolic activity of splenocytes and bone marrow cells at lower concentrations compared with fibroblasts (unpublished data). This observation is of huge importance due to the presence of experimental evidence on the inability of carrageenans to be absorbed and their interaction with host intestinal immune cells [4, 20, 27]. In particular, there is some evidence that high-molecular-weight carrageenan can overcome the intestinal barrier via macrophages in Peyer's patches [28].

It has been reported that carrageenan toxicity is mediated by the TLR4-and NF-kB-associated pathways, NLRP3 inflammasome pathway, ROS-mediated damage and, hence, upregulation of pro-inflammatory cytokines [25, 29-31]. The role of pathways outlined above in immune cells is more pronounced compared with fibroblasts, which can be speculated to explain the difference in cytotoxic effects of semi-refined carrageenan on different types of cells. However, more cell culture-based and animal studies should be carried out to elucidate molecular mechanisms by which carrageenans exert their pro-inflammatory activities.

Conclusion

Semi-refined carrageenan (E407a) shows cytotoxic properties to skin fibroblast cell cultures at high concentrations.

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Coronavirus disease 2019 and preterm birth: A systematic review and meta analysis

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Abstract

Background: The Coronavirus disease 2019 (COVID-19) has been a challenge for the healthcare system in most countries and its association with adverse pregnancy outcomes, especially preterm birth is controversial. The present study aims to understand the relation between severe acute respiratory syndrome coronavirus 2 infection of pregnancy and outcome of preterm birth.

Material and methods: A search was performed in Cochrane Library, PubMed, Scopus, E library and local databases up to 30 April, 2021. Searching strategy was used PICOS (Population, Intervention, Comparison and Outcomes, Study design) framework. Study group included COVID-19 pregnant patients compared with healthy pregnant women. Main outcome was perform birth (< 37 gestational week). The data were extracted from two authors and statistical analyses carried out using Review Manager (RevMan). Random-effects meta-analysis was conducted to calculate odds ratios (ORs) and weighted mean differences with 95% confidence intervals (CI).

Results: Twenty six cohort studies involving 436695 pregnant participants were included in this study. COVID-19 was associated with significantly increased risk of preterm birth [OR =1.30, CI = 1.20 to 1.39; p = 0.02; I2 = 41%].

Conclusion: COVID-19 may be associated with increased risks of preterm birth, it is important to further understand the mechanism that explain the association and identify effective prevention methods to avoid COVID-19 caused adverse pregnancy outcome.

Key words: COVID-19, Premature Birth, SARS-CoV-2

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic is a challenge for the healthcare system in most countries with more than 160 million COVID-19 cases and 3.4 million deaths worldwide. The current outbreak of coronavirus disease 2019 (COVID-19) was first emerging in Kazakhstan on 13th March 2020 and quickly spread over all territories of the country [1]. The obstetric health care has always been an area of increased responsibility for the life and health of the mother and her child. Clinical protocols, standards and guidelines for managing pregnancy and childbirth are urgent in such a pandemic. In the Republic of Kazakhstan, up to 1st September, 2020, the registered number of pregnant COVID-19 cases reached to 4851, 3473 of which were pregnant, 1378 of which were postpartum, COVID-19 was confirmed in 8.75% of the newborns, 35.7% of infected newborns were born prematurely [2] and data from Russia, suggested that preterm birth rate of COVID-19 patient was 18.3% [3]. Findings from a multi-center study in Washington reported a higher infection rates in pregnant women coupled with an elevated risk of morbidity and maternal mortality [4]. High rate of adverse pregnancy outcomes including preterm birth among pregnant women with COVID-19 were reported in our country and worldwide [2, 4].

Pregnant women and their fetuses are more predisposed to infectious disease outbreaks and infection-associated morbidity and mortality, especially in the absence of established therapies [5]. In addition, disruption of health-care services and lack of attendance in health-care facilities may have indirect negative

impact on pregnancy outcomes. It's reasonable to believe that respiratory pathogens pose a threat to pregnant women, due to more cardiopulmonary burden than non-pregnant women. Although current observational data have described respiratory symptoms similar to the general population and large majority of cases are asymptomatic [3, 4], the hospital and intensive care unit (ICU) admission rates of pregnant women with the disease are higher than unaffected pregnant women [6]. Demographic factors, such as age, race, socioeconomic status, increased body mass index and preexisting comorbidity increase the risk of severe or critical COVID-19 symptoms and special clinical management, such as ICU, invasive ventilation, and extra corporeal membrane oxygenation [7]. In addition to the impact of COVID-19 infection on a pregnant woman, there are also concerns about possible effects on the fetus and newborn; for these reasons, mother to fetus vertical transmission of the SARS-CoV-2 has been required special attention. However, Available evidence warrants the mother to fetus vertical transmission of the SARS-CoV-2 is negligible [8].

Preterm births are the most common adverse pregnancy outcomes which can lead to neonatal complications and it is considered as the leading cause neonatal mortality and morbidity [9]. In Kazakhstan, the rate is as high as 15.2% in 2017 compare to 8.8% reported in 2010 [9]. Infectious diseases concomitant with inflammation play a key role in preterm parturition among current researched multifactorial etiology [9]. As a special population, SARS-CoV-2 infected pregnant women may be at higher risk for worse pregnancy outcomes when compared to the healthy matches [10, 11]. The possible effect on pregnancy and birth outcomes were reported inconsistently [12, 13]. An increased frequency of preterm births and caesarean deliveries in pregnant patients with COVID-19 was reported [14, 15]. However, SARS-CoV-2 related risk of preterm birth is conflicting. Limitation of population representativeness, sample size, lack of appropriate comparison may affect the variety of the results. To better understand the potential effect of the SARS-CoV-2 on pregnancy outcomes, the well-designed studies are essential which include pregnant women with and without COVID-19 in matches.

A systematic review and meta-analysis was conducted to review the impact of the COVID-19 on pregnancy outcomes to further understand the association between COVID-19 and adverse pregnancy outcomes.

Materials and methods

Searching and screening methods

PRISMA statement guidelines was used to instruct the present study [16]. The following data bases were used for access the available evidence: Cochrane Library, PubMed, Scopus, Google Scholar E library and local databases. "COVID-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2 OR 2019 novel coronavirus" AND "pregnancy outcomes OR preterm birth OR preterm delivery OR preterm labor " were used as search terms. All available observational studies published before 30th of April were included in this study. PECOS framework, including Population, Exposure, Comparison, Outcomes, and Study design, was used as a search strategy tool. Literature and systematic reviews, meta analyses, case reports, and case series were excluded from the study.

Methodological quality of the screened studies was independently assessed by two reviewers. The third reviewer was involved to get consensus. The following information was extracted from the included studies: the first author's last name, and countries of origin. Newcastle-Ottawa Scale (NOS) was used to assess the quality of included cohort and case control studies. Sample representativeness, study subjects recruitment methods, case and control comparability, confounding variables were evaluated and enrolled respectively high and moderate-quality studies. Newcastle-Ottawa Scale contains 8 items within 3 domains and the total maximum score is 9. A study with score from 7 to 9 has high quality, with score from 4 to 6 has high risk, and with score from 0 to 3 has very high risk of bias.

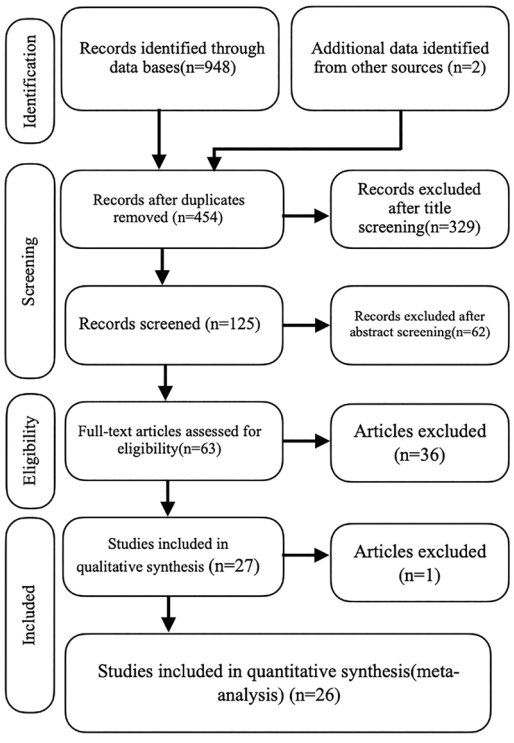
Data analysis

The data were extracted and statistical analyses carried out using Review Manager (RevMan) 5.4. We used unadjusted estimates for meta-analysis and Mantel– Haenszel method to combine data on dichotomous outcomes, and measures of effect are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity with the I2 statistic was used for the data evaluation and consideration for whether apply random effects model or a fixed effect model. When the value of $p<0.05$, we considered statistically significant.

Results

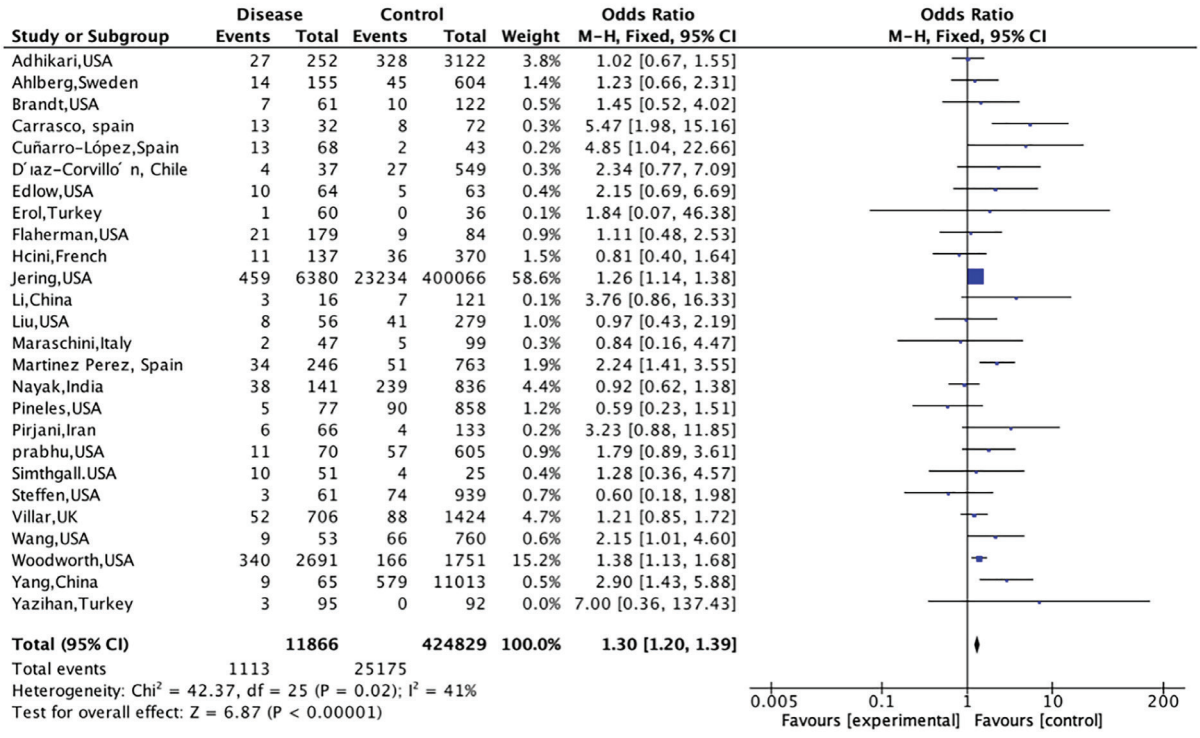
The search strategy resulted in 454 potentially relevant citations. We 391 excluded citations by screening the title and abstract. The PRISMA Flow Diagram (Figure 1) summarizes the process of literature search and selection of studies. After screening the titles and abstracts, we read 63 full-text papers and enrolled 26 studies with comparable outcomes [11-15, 17-36] and 10 of them were prospective cohorts, 13 were retrospective cohorts, 4 were case control studies.

Figure 1 - Flow diagram of the study search and identification



Of the 436695 pregnant participants, 11866 SARS-CoV-2 infected pregnant women and 424829 unaffected pregnant controls assessed for the SARS-CoV-2 on preterm birth in this systematic review and meta-analysis, compared with pregnant women without SARS-CoV-2 infection , the affected pregnant women were at higher risk of experience preterm birth (OR 1.30, 95% CI 1.20 to 1.39; $I^2 = 41\%$; 26 studies) (Figure 2).

Figure 2 - Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between coronavirus disease 2019 (COVID-19) and preterm birth. (patients with COVID-19 versus patients without COVID-19)



Discussion

At present, to understand the potential adverse effects of the disease on the course of pregnancy, perinatal outcomes, fetal health are critical to provide evidence-based recommendations to antenatal and obstetrical health care for pregnancy-specific administration and monitoring. This systematic review focuses on analysis the available global and local data on the effects of the COVID-19 pandemic on most prevalent pregnancy outcome, preterm birth. Our present study involved 436695 pregnant participants from different countries. Our result found COVID-19 in pregnancy is associated with preterm birth compared with no COVID-19 pregnancies. This finding suggests that health care system should be aware of the adverse outcome to manage, administer and monitor pregnancies in patients with COVID-19 and adopt effective strategies to prevent or reduce risks of adverse pregnancy outcomes.

The number of publications on COVID-19 in pregnant people continues to increase, along with the further understanding the nature of the virus. Case reports and case series were reviewed in the early stage of the pandemic, followed by systematic reviews included good-quality data, were well summarized the antenatal care and fetal surveillance clinical futures, maternal-fetal complications, vertical transmission status, treatment options and the possible negative effects on maternal and fetal outcomes [37, 38]. However, the data with regards to preterm birth is conflicting. A meta-analysis of recent good-quality cohort and case control studies suggested that COVID-19 is associated with a considerable risk of adverse pregnancy outcomes such as preterm birth, low birth weight and preeclampsia, and the risk was increased with the disease severity [38]. Another systematic review only involved the cohort studies which was consisted of positive cases with contemporaneous controls with negative test results to reduce the selection bias suggested a contrary conclusion regarding with preterm birth [37]. The original studies which were reported the relation of COVID-19 to adverse pregnancy outcomes had a different research design. Some studies used inappropriate control groups which included non-pregnant general population or without a comparison group, some of them didn't considered baseline of the selected population or confounding factors. This may confuse the effects of the virus.

The strengths of our study include the comprehensive search on the last global and local data which included appropriate comparisons, and included and synthesized a broad range of literature. Our findings suggest that local or neighbor studies are needed for contributing the international database after we screened the methodological part and design of the original studies.

Our meta-analysis also suggests that SARS-CoV-2 infection was associated with preterm birth compared with the absence of SARS-CoV-2 infection. The mechanisms underlying the association between COVID-19 and preterm birth are unclear, but the studies have shown that the pathogen may cause exaggerated systemic inflammatory responses which may disturb the optimal status of placenta for fetal growth and development [39]. Vascular malperfusion of the placenta-fetal unit may be the another contribution factor for developing the adverse pregnancy outcomes [40]. A recent study in the Netherlands found that COVID-19 mitigation measures were associated with a reduced incidence of preterm birth may suggested the adverse pregnancy outcomes may be influenced by changes of obstetric management during the pandemic condition. However, the reason for preterm birth was not clear, including if preterm birth was medically indicated or spontaneous.

Our study is limited by the inconsistency research design and heterogeneous quality of included studies. Preterm birth and COVID-19 infection have some major confounding factors like race/ethnicity, socioeconomic status, comorbidity like hypertension and diabetes which may bias the estimates. We enrolled studies regardless of the prospective and retrospective

design and baseline of the sample, this may increase the bias which caused by variety of adjusted and unadjusted estimates. The nature of observational studies contributes to the possibility of residual confounding. Secondly, the inconsistency of research population among the enrolled studies. In addition, our literature search was restricted to publications in Russian, Kazakh and English. Future studies are needed to collect more robust data to further validate or substantiate these findings, better understand the pathophysiologic pathways that explain these associations and identify effective strategies to prevent adverse outcomes in pregnant people with COVID-19.

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Is pain perception different in pediatric and adult patients undergoing stone crushing procedure after the application of multimodal analgesia?

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Abstract

Aim: Extracorporeal shock wave lithotripsy (ESWL) is an important modality in the treatment of urinary system stone disease in children and adults. However, ESWL may be painful and stressful procedure. We aimed to examine the differences between pain perception felt during ESWL in pediatric and adult patients after the application of multimodal analgesia.

Material and methods: Patients who underwent the stone crushing procedure under multimodal analgesia at the ESWL unit of Mersin University Hospital Urology Clinic between May 2010 and December 2010, were divided into two groups as pediatric and adult. Using the VAS (Visual Analog Scale) form, the adult patients' and pediatric patients' pain perception felt during ESWL, were scored and compared.

Results: The success rate for ESWL was calculated as 83.3% for the pediatric group and 80% for the adult group. The first, second and third ESWL sessions mean VAS scores were 4.54±1.13, 4.55±1.11, 4.53±1.14 for pediatric group and 3.58±1.18, 3.56±1.20, 3.57±1.19 for the adult group. There was no statistically significant difference between the 1st ESWL session, 2nd ESWL session and 3rd ESWL session mean VAS scores in the pediatric group or adult group ($p>0.05$). But the 1st ESWL session, 2nd ESWL session and 3rd ESWL session mean VAS scores of the pediatric group were found to be statistically significantly higher than the adult group ($p<0.05$).

Conclusion: ESWL is a painful procedure. Our ESWL success rate is compatible with the literature. The pediatric and adult patients successfully completed the ESWL procedure with multimodal analgesia. ESWL sessions have no effect on each other for the pain perception felt during ESWL but the pain perception felt during ESWL score was higher in pediatric cases.

Key words: extracorporeal shock wave lithotripsy, pain perception, Visual Analog Scale, multimodal analgesia

Introduction

The incidence of renal stone disease varies between 1-20%, and countries where it reaches up to 37% are followed [1, 2]. Pediatric stone disease accounts for 2-3% of all stone disease cases and ıt is most common in children of both sexes, equally between the ages of 5 and 7 years [3].

Symptoms of renal stone-related flank pain, abdominal pain, urinary infection and hematuria can be seen. If the treatment of renal stone is not performed at the appropriate time, secondary diseases due to pain, urosepsis, renal dysfunction and end-stage renal failure may also be observed [4]. Medical and interventional treatment procedures are available for the treatment of renal stone disease. ESWL is highly preferred in the interventional treatment procedure [4].

Extracorporeal shock wave lithotripsy (ESWL), which has been successfully applied for many years, is an important modality in the treatment of pediatric and adult urinary system stone disease [5]. Compared to minimally invasive and invasive methods, ESWL has many advantages in the treatment of kidney stones, such as fast recovery, less side effects, low kidney injury rate, and ease of re-treatment [6].

During the ESWL procedure, as a subjective feeling that is difficult to define, pain is sometimes described by patients with an intensity that may require general

anesthesia in addition to the application of analgesic and sedo-analgesic agents [7]. It is known that anxiety before ESWL increases and continues during the procedure has an effect on this pain. In order for the stone to crush easily during ESWL, the fact that the patient is cooperated and does not feel pain is important in increasing the effectiveness of ESWL [7].

The pain related to ESWL is complex acute pain. Multimodal analgesia is recommended in complex acute pain management. Pharmacological agents, regional anesthesia, rehabilitation, cognitive behavioral therapy, increasing morale, and non-pharmacological methods are recommended for this treatment [8, 9]. Failure to prevent or minimize treatable procedural pain in children is now considered both inappropriate and unethical [10]. Visual Analog Scale (VAS) has been widely used in studies to evaluate acute pain severity. The VAS form has proven itself for a long time and is a test that has been accepted in the world literature. It is safe, easy to apply [11].

In our retrospective study, we aimed to evaluate the pain perception felt during ESWL with recording VAS scores in children and adult patients after the application of multimodal analgesia and also to compare the both group's pain perception felt during ESWL .

Material and methods

Child and adult patients who applied to Mersin University Hospital Urology Clinic, were diagnosed with urinary system stone disease as a result of the tests and underwent ESWL for one to three sessions with ten days intervals were included in the study. All patients had symptoms related to an average of 1-2 cm renal stones without urinary infection. All the stones were radio-opaque. The patients were divided into two groups as pediatric (n: 18) and adult (n: 20). ESWL was applied to 38 renal units. After a physical examination and before ESWL, urine analysis and urine culture, serum urea, creatinine and electrolyte level, complete blood count, prothrombin (PTT) and aPTT level measurements were undertaken in all patients. ESWL was performed after successful antibiotic therapy in the patients that were found to have a urinary infection. ESWL contraindications (pregnancy, bleeding diathesis, severe skeletal system malformation, and obesity that would not allow the procedure) were also used as exclusion criteria. Previous ESWL treatment and psychiatric illness diseases were also an exclusion criteria.

Application of multimodal analgesia and ESWL: 40 minutes before the procedure intramuscular diclofenac sodium (0,5-2 mg/kg for pediatric patient) was administered to patients, and then the assistant physician responsible for the ESWL unit had told how to perform the procedure with the device to the patient and the procedure was followed at the time of another patient's treatment. A Multimed classic device (Elmed, 2010, Turkey) was used for ESWL. For the procedure, the pediatric patients received an average of 1,700 waves (1,500-2,000) and a maximum of 15Kv while the adults were applied 2,300 waves (1,500-2,500) and a maximum of 18Kv. The processing time was 40 minutes. At the 20th minute of the procedure, the VAS score that the patient felt was written by the assistant physician. There is a 10 cm ruler in the VAS form with painlessness on one end and the most severe pain on the other. The place marked by the patient on the ruler indicates his/her own pain. It is a one-dimensional method of measuring pain [8]. After the procedure, the patients were kept under observation for two hours.

At the end of the first week, the patients were evaluated with urinalysis, direct urinary tract radiography, and urinary ultrasonography. In cases where the stones were not fragmented, or fragmentation was not sufficient, the patients were called for a further ESWL session.

The mean VAS scores of the first, second and third ESWL sessions were calculated for the pediatric and adult groups. The mean VAS scores of the same ESWL sessions of both groups were compared, and the mean VAS scores of each group due to three different ESWL sessions were compared within their own groups. By analyzing VAS scores related to ESWL sessions, we aimed to examine the differences between pain perception felt during ESWL in pediatric and adult patients after the application of multimodal analgesia.

IBM SPSS Statistics 22.0 program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (Mean, Standard deviation), Friedman's S test was used for the analysis of variance between repeated measurements of quantitative data that did not show normal distribution, and Wilcoxon Signed Ranks test was used for the analysis of the difference between repetitions. Significance was evaluated at the $p<0.05$ level.

Results

Pediatric group included 10 boys and eight girls, with a mean age of 12.94±2.63 years and adult group included 14 males and six females, with a mean age of 46±9.25 years. Body mass index (BMI) was 25.68±4.63 in the adult group and it was 23.34±27 in the pediatric group. In the pediatric group, eighteen patients completed first ESWL session, ten patients completed second ESWL sessions and four patients completed third ESWL session. In the adult group, twenty patients completed first ESWL session, fourteen patients completed second ESWL sessions and six patients completed third ESWL session. The success rate was calculated as 83.3% for the pediatric group and 80% for the adult group.

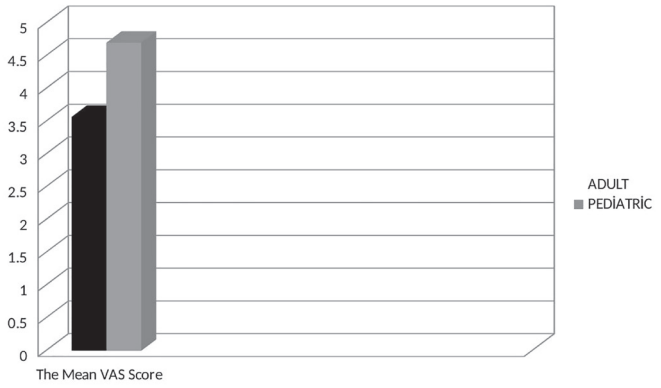
Table 1 presents the comparison of the VAS Scores related to ESWL Sessions between and within the Pediatric Group and Adult Group.

Table 1 Comparison of the VAS Scores related to ESWL Sessions between and within the Pediatric Group and Adult Group

VAS Score	Pediatric Group	Adult Group	1p
	Mean ± SD	Mean ± SD	
1st ESWL	4.54±1.13	3.58±1.18	0.001**
2nd ESWL	4.55±1.11	3.56±1.20	0.001**
3hd ESWL	4.53±1.14	3.57±1.19	0.001**
2p	1.000	1.000	
3p 1st ESWL- 2nd ESWL	1.000	1.000	
3p 1st ESWL- 3hd ESWL	1.000	1.000	
3p 2nd ESWL-3hd ESWL	1.000	1.000	

For comparison of the same ESWL session's mean VAS score between the groups: The first ESWL session mean VAS score of the pediatric group was found to be statistically significantly higher than the adult group ($p<0.05$). The second ESWL session mean VAS score of the pediatric group was found to be statistically significantly higher than the adult group ($p<0.05$). The third ESWL session mean VAS score of the pediatric group was found to be statistically significantly higher than the adult group ($p<0.05$).

Figure 1 - The chart of the mean VAS scores of the pediatric and adult patient groups.



For comparison of the different ESWL sessions' mean VAS scores within the same group: In the pediatric group; There was no statistically significant difference between the mean VAS 1st ESWL session, 2nd ESWL session and 3rd ESWL session scores ($p>0.05$). In the adult group; There was no statistically significant difference between the mean VAS 1st ESWL session, 2nd ESWL session and 3rd ESWL session scores ($p>0.05$).

Discussion

In children, ESWL has high efficiency and reliability with a high success rate [12]. It is also applied with a high success rate in adult patients [13].While the success rate is affected by stone size, density and localization in pediatric patients, in adult cases, in addition to these factors, body mass index and skin-stone distance are also effective [12,14]. In our retrospective study, the success rate of ESWL for 1-2 cm sizes radio-opaque renal stones without in pediatric and adult groups were followed in accordance with the literature and also no abnormality were observed in the BMI ratios of both groups.

In health interventions, exposure to severe pain without adequate pain management may lead to long-term negative consequences, such as morbidity and mortality, as well as fear and avoidance of future medical procedures [15]. Therefore, adequate pain management is essential for pediatric patients aged 0 to 17 years [16]. Different methods of analgesia, especially sedo-analgesia, have been applied in pediatric patients during ESWL in order to reduce the morbidity related to the procedure and ensure patient compliance. Fentanyl or midazolam is used for sedation and ketamine for analgesia [17]. General anesthesia may also be required for pediatric cases with pain intolerance. ESWL has been successfully performed with intramuscular analgesics (diclofenac sodium) in children over 12 years of age [18]. In a study by Gönener et al. [19], it was observed that giving descriptive and introductory information about the procedure to school children increased their pain threshold and decreased their fear in relation to the procedure. In our study the mean age of pediatric patients was 12.98. The patients completed the ESWL procedure after the application of multimodal analgesia (descriptive and introductory information + intramuscular diclofenac sodium). There was no need for sedo-analgesia or general anesthesia in any of the cases.

Some studies showed that informing adult patients undergoing ESWL about the procedure played an important role in reducing their pain score, as well as increasing their level of understanding about the process [20,21]. Thus, the anxiety intensity of adult patients decreases [22,23]. There are also studies investigating the primary preference of non-steroid anti-inflammatory drugs (NSAIDs) during ESWL. In a meta-analysis comparing NSAIDs and opioids, the two groups of drugs were observed to equally relieve pain during ESWL [24]. In another study conducted by Özkan et al., it was reported that lornoxicam (an NSAID) administered before ESWL had a better analgesic effect than paracetamol and tramadol [25]. In addition, in a study on renal colic pain treatment, NSAIDs were concluded to be stronger analgesics with fewer side effects compared to opioids [26]. In our study, the adult patients completed the ESWL procedure after the application of multimodal analgesia (descriptive and introductory information + intramuscular diclofenac sodium).

The VAS form is accepted as a safe, valid and usable measurement tool for repeated measurements. There was no significant difference in the responses given after the test's short intervals and repetitions [27]. In studies conducted for the treatment of experienced pain due to ESWL, no significant difference was detected in the VAS scores measured more than once [20,22]. . De Sio et al evaluated the pain tolerability in ESWL sessions with a relatively newer machine, and nearly half of the cases scored their pain on a VAS as 4 or 5 [28]. In our study, since the desired scores were answered with in a certain short period of time, we received only one answer in the tests we repeated. The first, second and third ESWL sessions mean VAS scores were 4.54±1.13, 4.55±1.11, 4.53±1.14 for pediatric group and 3.58±1.18, 3.56±1.20, 3.57±1.19 for the adult group. There was no statistically significant difference between the 1st ESWL session, 2nd ESWL session and 3rd ESWL session mean VAS scores in the pediatric group or adult group ($p>0.05$).

The child is physiologically and cognitively immature, but a developing creature, not a miniature of the adult. The physical, cognitive and emotional reactions to the disease vary according to the developmental period, and everything that affects the family as a system also affects the child [29]. Anatomical differences, physiological differences and behavior patterns towards the disease between children and adults affect an important role in the pain perception [30]. Hasanpoura found that pain perception decreased with increasing age in his research with children aged 5-12 years [31]. In another study, they argued that pain perception decreased as a result of the development of pain control methods with increasing age [32,33]. In our study all the same ESWL sessions mean VAS scores of the pediatric group were found to be statistically significantly higher than the adult group ($p<0.05$).

Conclusion

ESWL is a painful procedure. In our study, Our ESWL success rate is compatible with the literature. Pediatric and adult patients successfully completed the ESWL procedure with multimodal analgesia. ESWL sessions have no effect on each other for the pain perception felt during ESWL but the pain perception felt during ESWL was higher in the pediatric group.

Ethics committee approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Vitamin D in obstructive sleep apnea syndrome follow up and treatment: A study of 482 cases

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Abstract

Aim: The aim of the study was to determine the factors associated with Obstructıve Sleep Apnea Syndrome (OSAS) severity and vitamin D deficiency by examining routine laboratory parameters in patients with OSAS without comorbidities. We also aimed to see whether the severity of OSAS increased with decreasing levels of vitamin D.

Material and methods: Patients who presented to Adana City Training and Research Hospital, Ear Nose Throat Clinic with the symptoms of snoring and sleep apnea and who underwent polysomnography (PSG) in the sleep laboratory of the Otorhinolaryngology Clinic were included in the study. Blood results were analyzed retrospectively from the hospital information system. The patients were divided into groups according to their Apnea hypopnea Index (AHI) values as simple snoring, mild OSAS, moderate OSAS, and severe OSAS. According to the vitamin D values, the patients were categorized as sufficient >30 ng/ml, insufficient 20-30 ng/ml and deficient <20 ng/ml.

Results: Out of the 777 patients examined 482 patients fulfilling the inclusion criteria were analyzed for the study. It was seen that severity of OSAS increased concomitantly with decreasing Vitamin D levels.

Conclusion: Vitamin D deficiency is observed in patients with OSAS and is related to the severity of the disease. We think that vitamin D therapy may be beneficial in reducing the severity of the disease.

Key words: obstructive sleep apnea syndrome, polysomnography, vitamin D, apnea hypopnae index, parathormone

Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent episodes of partial or complete obstruction in the upper airway during sleep and increased respiratory effort, oxygen desaturation, sleep interruption, and excessive daytime sleepiness. Clinically, snoring is the most prominent symptom in patients with OSAS. Apart from snoring, nighttime symptoms such as apnea, nocturia, night sweats, dry mouth, frequent awakening, and daytime symptoms such as headache, excessive daytime sleepiness, concentration disorder, cognitive and mood changes are observed. OSAS affects 3-9% of middle-aged women and 10-17% of men [1]. Obesity, advanced age, menopause, anatomic disorders of the head and neck, male sex, smoking, alcohol, and sedative drugs play a role in the development of OSAS [2]. Psychiatric symptoms such as cognitive impairment, depression, irritability, and anxiety may appear as the referral symptoms of OSAS. To diagnose OSAS, which can cause serious health problems, there is no biochemical parameter other than a detailed anamnesis taken during clinical evaluation and physical examination is insufficient. Therefore, in addition to clinical evaluation, the presence of sleep-related breathing disorder should be demonstrated objectively for diagnosis.

Currently, the gold standard diagnostic test in the diagnosis of respiratory-related sleep disorders is polysomnography (PSG) performed in the sleep laboratory [3]. However, we know that in clinical practice, sleep disorders are diagnosed late due to various reasons such as the increase in patient density and insufficient training in primary care medicine, and therefore delays in treatment. Sympathetic activation, endothelial dysfunction, systemic inflammation, and hypercoagulability occur with hypoxia-reoxygenation attacks in patients with OSAS. As a result, various endocrinopathies such as high blood pressure, high glucose, increased waist circumference, low high-density lipoprotein (HDL), high triglyceride levels, and osteoporosis can be seen [4,5].

Vitamin D is a fat-soluble vitamin that plays a role in bone and mineral metabolism. Vitamin D is taken into our body orally with food or is created in the skin by sunlight [6]. Serum 25-hydroxy vitamin D levels are used to determine vitamin D levels in our body [7]. Vitamin D deficiency results in a decrease in intestinal calcium absorption, leading to a decrease in serum calcium concentration. Vitamin D plays a role in the regulation of bone metabolism and calcium homeostasis. In addition, vitamin D receptors play an important role in the regulation of changes in the sleep-wake cycle in many brain regions including the hypothalamus. Low Vitamin D levels in the blood cause weakness in the skeletal and muscular system [8]. In Vitamin D deficiency, musculoskeletal functions deteriorate and the incidence and severity of OSAS increase due to the decrease in muscle tone in the upper respiratory tract [9]. Low Vitamin D levels are associated with airway inflammations such as rhinitis, adenoiditis, tonsillar hypertrophy, and this increases the severity of OSAS [10,11].

Different results were obtained in studies examining the relationship between OSAS and vitamin D in the literature. The aim of the study was to determine the factors associated with Obstructıve Sleep Apnea Syndrome (OSAS) severity and vitamin D deficiency by examining routine laboratory parameters in patients with OSAS without comorbidities. We also aimed to see whether the severity of OSAS increased with decreasing levels of vitamin D.

Materıal and methods

Patients who presented to Adana City Training and Research Hospital, Ear Nose Throat Clinic with the symptoms of snoring and sleep apnea and who underwent PSG in the sleep laboratory of the Otorhinolaryngology Clinic between June 2019 and December 2019 were included in the study. Before PSG, blood is routinely taken from patients for a hemogram and biochemistry tests to determine the presence of any endocrinologic disorders. İnclusion criteria are; patients without diabetes mellitus (DM), coronary artery disease (KAH), hypertension (HT), metabolic syndrome (MS), cancer, autoimmune diseases, musculoskeletal disease, cerebrovascular diseases (SVO). Patients whose blood results were registered in the hospital information system were included in the study. Patients who had any disease that could affect vitamin D and PTH levels or who used vitamin D externally were excluded from the study.

Before the PSG test, blood samples were taken from all patients (12 hours fasting) for the measurement of vitamin D serum levels and other biochemical parameters. After coagulation, the tubes were centrifuged and kept at -80°C until required for analysis. Serum vitamin D was measured by ARCHITECT 25 (OH) D chemiluminescent microparticle immunoassay (Abbott Diagnostics, Wiesbaden, Germany) [12]. This method is an automated calibration instrument system consisting of an immunoassay for the quantitative measurement of 25 (OH) D. PSG and blood results were analyzed retrospectively. The study was approved by Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: July 1st, 2020; Decision: 963).

PSG recordings of all patients were evaluated retrospectively and cross-sectionally. Sleep and physiologic variables were monitored using a Comet-PLUS Grass® (Astro-Med Industrial Park, West Warwick, USA) PSG. Electroencephalography (EEG) with 10 channels (C3, C4, O1, O2, Fp1, Fp2, F3, F4, P3, P4), submental electromyography (EMG), right and left eye electrooculography (EOG), electrocardiography (ECG), oronasal airflow (thermal sensor and nasal pressure transducer), body position, thoracic and abdominal motion meter (inductance plethysmograph), arterial blood oxygen saturation measurement with finger pulse oximetry, left and right leg motion sensors (EMG) , and a tracheal microphone were used.

Apnea was defined as a reduction of more than 90% in the airflow signal measured by the thermal sensor for at least 10 seconds. Hypopnea was defined as a decrease in nasal pressure signal for at least 10 seconds, more than 30% compared with basal, and resulting in desaturation or arousal more than 3% compared with basal. The AHI value is obtained by dividing the sum of the apnea and hypopnea numbers by the person's sleep time. Thus, the AHI in 1 hour is revealed Apnea-Hypopnae Index (AHI) 0-4.9 = simple snoring, AHI 5-14.9 = mild OSAS; and AHI: 15-29.9 were evaluated as moderate OSAS, and AHI >30 as severe OSAS. The patients were divided into groups according to their AHI values as simple snoring, mild OSAS, moderate OSAS, and severe OSAS. BMI was calculated by measuring height and weight by the same person using sensitive scales and a tape measure in the outpatient clinic.

Blood results were analyzed retrospectively from the hospital information system. The patients' Vitamin D, parathormone (PTH), total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), ferritin, thyroid-stimulating hormone (TSH), B 12, and hemoglobin (HGB) values were recorded by the same person. According to the vitamin D values, the patients; Cathogarized as sufficient >30 ng/ml, insufficient 20-30 ng/ml and deficient <20 ng/ml.

The analysis of the data was performed using the SPSS 22.0 package program. Demographic information and clinical characteristics of patients p1: Kruskal Wallis test, p2: Chi-square test (percentages are evaluated according to rows) * It was made with the Linear-by-Linear Association and mean-median values were given. The hemogram and biochemistry values of the patients were compared with the Kruskal Walls test according to the groups and the median-mean values were determined. Multiple Binary Logistic Regression between Mild+moderate+severe OSAS with simple OSAS was done. P<0.05 was considered significant.

Results

Out of the 777 patients examined 482 patients fulfilling the inclusion criteria were analysed for the study. 87 patients were evaluated as simple snoring, 133 patients as mild OSAS, 102 patients as moderate OSAS, and 160 patients as severe OSAS (Table 1).

Medians of age differ according to AHI groups (p=0.002). Accordingly, this difference is between the simple snoring and severe OSAS groups (p<0.05).The average age of the severe OSAS group is the highest. BMI medians differ according to AHI groups (p<0.001). Accordingly, this difference is between the simple snoring and moderate and severe OSAS, mild and severe OSAS, moderate and severe OSAS (p<0.05). Severe OSAS group with the highest BMI. A significant relationship was found between AHI and gender (p=0.021). Accordingly, the rate of males in the severe OSAS was higher than the simple snoring ,mild and moderate group, and the rate of males in the moderate OSAS was higher compared to the simple snoring (p<0.05).The group with the highest male gender is the severe OSAS group. A significant relationship was found between AHI and smoking (p=0.021). Accordingly, the proportion of smokers in the sever OSAS was higher than that of the simple snoring, mild and moderate group, and the proportion of smokers in the moderate OSAS group was higher than that of the simple snoring (p<0.05).The highest smoking rate is in the severe OSAS group.

Table 1 Demographic, lifestyle and clinical characteristics of study subjects by severities of OSAS

	Total (n=482)		Simple snoring (n=87)		Mild OSAS (n=133)		Moderate OSAS (n=102)		Severe OSAS (n=160)		p1
	Median [IQR] Mean(SD)		Median [IQR] Mean(SD)		Median [IQR] Mean(SD)		Median [IQR] Mean(SD)		Median [IQR] Mean(SD)		
Age	45.13±11.07 45 [37.5-53]		41.38±11.54 43 [33-49]		45.07±10.43 45 [37-52]		44.58±11.14 46 [38.75-51.25]		47.58±10.74 47 [40-55]		0.002
BMI	29.9±6.03 29 [27-32]		28.46±7.51 28 [25-29]		28.73±4.28 28 [26-30]		29.56±4.82 29 [27-31]		31.88±6.59 31 [29-35]		<0.001
	N	%	n	%	N	%	n	%	n	%	p2
Sex											
Male	358	74.3	50	58.6	90	68.4	76	74.5	139	87.5	<0.001
Female	124	25.7	36	41.4	42	31.6	26	25.5	20	12.5	
Smoking											
No	291	60.4	67	77.0	90	68.4	60	58.8	73	45.6	<0.001
Yes	191	39.6	20	23.0	42	31.6	42	41.2	87	54.4	
Vitamin D											
Deficiency	336	69.7	54	62.1	94	70.7	70	68.6	118	73.8	0.021*
İnsufficiency	111	23.0	24	27.6	27	20.3	21	20.6	39	24.4	
Sufficiency											
	35	7.3	9	10.3	12	9.0	11	10.8	3	1.8	

p1: Kruskal Wallis test, p2: Chi-square test (percentages are evaluated according to rows) * Linear-by-Linear Association
BMI:Body mass index

A significant relationship was found between AHI and vitamin D levels (p=0.021). Accordingly, the ratio of simple snoring, mild and moderate OSAS was higher in the sufficiency group than the heavy OSAS (p<0.05). Vitamin D is deficient in 73.8% of the severe OSAS group, 68.6% of the moderate OSAS group, and 62% of the mild OSAS group.The group with the highest vitamin D deficiency is the severe OSAS group (Table 1).

Total Cholesterol medians differ according to AHI groups (p=0.003). Accordingly, this difference is between the simple snoring and moderate and severe, mild and severe OSAS (p <0.05). The highest cholesterol levels were seen in severe OSAS . Triglyceride medians differ according to AHI groups (p<0.001). Accordingly, this difference is between the simple snoring and mild, mild and severe, moderate and severe OSAS (p<0.05). The highest Triglyceride levels were seen in severe OSAS. HDL medians differ according to AHI groups (p=0.009). Accordingly, this difference is between severe and mild and moderate OSAS (p<0.05). The highest HDL levels were seen in mild OSAS. HGB medians differ according to AHI groups (p=0.009). Accordingly, this difference is between the simple snoring and severe OSAS (p<0.05). The highest hemoglobin levels were seen in severe OSAS. The group with the lowest vitamin D level is the severe OSAS group (Table 2).

Table 2 Hemogram and biochemistry values of study subjects according to the severity of OSAS

	Total (n=482)		Simple snoring (n=87)		Mild OSAS (n=133)		Moderate OSAS (n=102)		Severe OSAS (n=160)		
	Mean(SD)	Median [IQR]	Mean(SD)	Median [IQR]	Mean(SD)	Median [IQR]	Mean(SD)	Median [IQR]	Mean(SD)	Median [IQR]	P
Parathormone	49.58 ±26.21	47 [33-60]	52.71± 41.91	47 [34-60]	48.84± 21.15	47 [33.25-63]	47.6± 23.65	45 [28-61.5]	49.74± 19.79	47 [35.25-60]	0.646
Total Cholesterol	223.21 ±176.98	200 [154-254]	200.39± 121.27	187 [123-221]	201.09± 86.97	200 [131-250]	218.27± 96.45	200.5 [157.25-242.25]	257.17± 270.24	210 [170-268]	0.003
Triglyceride	228.44 ±151.99	193 [129.75-276.25]	188.13± 150.35	145 [99.5-228.5]	211.75± 131.65	183 [115.5-274.5]	226.26± 126.93	201 [149.75-266.75]	265.16± 174.76	215.5 [158.25-308.25]	<0.001
LDL	139.44 ±41.05	141 [115-161.5]	132.88± 44.79	121 [100-154.5]	141.06± 46.82	148 [111.25-169.75]	140.03± 38.4	143 [116.75-163]	141.28± 35.24	141 [123-160]	0.036
HDL	47.94± 23.82	43 [37-50]	45.47± 15.45	43 [37-50.5]	51.19± 27.09	45 [38.5-52]	50.03± 25.74	44.5 [37.75-50]	45.26± 23.15	40 [36-48]	0.009
Ferritin	70.83± 66.2	50 [23-93]	63.17± 65.12	44 [20-86]	64.55± 58.89	45 [25-85]	70.43± 64.93	55.5 [21-91]	80.52± 72.44	56 [29.5-110]	0.073
TSH	1.74± 3.07	1 [0.9-2]	1.45± 1.06	1 [1-2]	1.47±1.11	1 [0.9-1.9]	1.74± 2.37	1 [0.9-1.95]	2.13± 4.82	1 [1-2]	0.618
B12 vitamin	220.92± 127.02	197 [144.25-257]	253.52± 176.25	203 [158.5-278]	213.59± 84.14	200 [149.5-260]	216.91± 135.91	192.5 [141.75-250.25]	211.99± 117.31	192 [137-250]	0.266
HGB	13.9±2.14	14 [13-15]	13.43± 2.12	14 [13-15]	13.98± 2.94	14 [13-15]	13.75± 1.53	14 [13-15]	14.18± 1.58	15 [13-15]	0.006
D vitamin	18.23±9.5	17 [12-22]	19.59± 10.77	18 [12-25]	18.67± 8.95	18 [12.5-22]	18.74± 10.61	15 [12-22]	16.79± 8.29	15.5 [11-21]	0.158

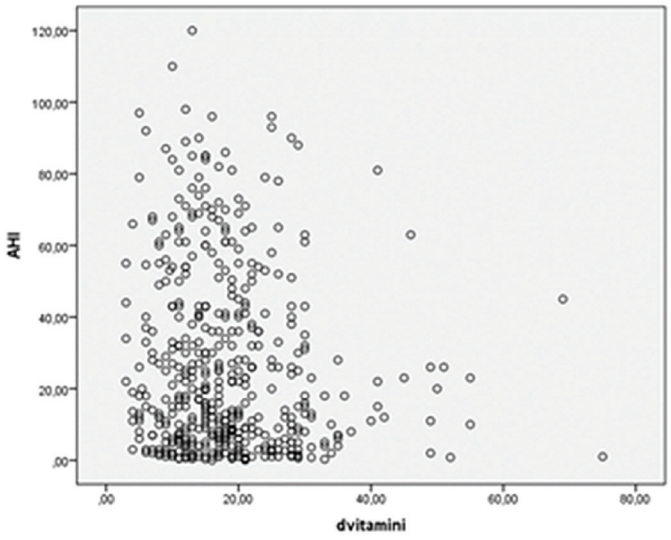
p: Kruskal Wallis test
LDL:Low-density lipoprotein cholesterol , HDL: high- density lipoprotein cholesterol TSH: Thyroid Stimulating Hormone
HGB:Hemoglobine

Table 3 Multiple Binary Logistic Regression between Mild+moderate+severe OSAS with simple OSAS

	Odds Ratio	95% C.I.for Odds Ratio		p
		Lower	Upper	
Age	1,037	1,014	1,060	0,001
Sex (female)	0,368	0,221	0,612	<0,001
Bmı	1,055	1,001	1,111	0,045
Vitamin d (deficient)	Ref.			0,123
Vitamin d (insufficient)	0,604	0,345	1,056	0,077
Vitamin d (sufficient)	0,554	0,236	1,303	0,176
Constant	0,315			0,167

p:Multiple Binary Logistic Regression

Figure 1 - Correlation of serum vitamin D level with apnea-hypopnea index (AHI) in all subjects



Age in mild+moderate+severe OSAS patients compared to simple OSAS patients 1.037, female 0.368 and BMI 1.055 times ($p<0.05$). Vitamin D level was not significant ($p>0.05$) (Table 3).

There is a very weak negative correlation between AHI and vitamin D ($r= -0.112$; $p=0.014$). Generally, as AHI increased, vitamin D level decreased (Figure 1). The mean AHI of the group with Vitamin D deficiency was 29.9, the mean AHI of the group with Vitamin D insufficient was 24.7, and the mean of the group with Vitamin D sufficient was 16.04.

Discussion

OSAS is an inflammatory disease with hypoxia and reoxygenation attacks. There are many studies in the literature investigating the relationship between OSAS and Vitamin D [12]. Vitamin D has an important role in the control of bone and mineral metabolism, and it is also effective in regulating the sleep-wake cycle because it has receptors at many points in the brain, especially in the hypothalamus. Since our study was performed on patients who came to the outpatient clinic with the suspicion of OSAS, Vitamin D deficiency was observed with a high rate of 69.7%. Vitamin D level decreased as the severity of OSAS increased. In addition, total cholesterol, Triglyceride, LDL and hemoglobin levels were higher in the severe OSAS group. No significant relationship was found in parathyroid hormone levels. Severe OSAS group had higher mean age, higher BMI and smoking rates.

Kul et al. found that vitamin D levels were significantly lower in patients with OSAS compared with the control group, but BMI and PTH levels were higher. The lowest vitamin D level and highest PTH level were found in the severe OSAS group. Therefore, eliminating vitamin D deficiency in these patients may reduce the severity of the disease and contribute to the treatment process [13]. As in our study, patients with OSAS had vitamin D deficiency and this rate was higher in patients with severe OSAS.

Vitamin D is a steroid hormone that plays an important role in Ca-P (phosphorus) metabolism and bone mineralization. Ethnic origin, physical activity, nutrition, smoking, obesity, and genetic reasons affect vitamin D metabolism. Çelikhisar et al. used the Berlin Sleepiness Questionnaire on city bus drivers and according to the survey, performed PSG on individuals at high risk for OSAS. According to the AHI values, patients with mild OSAS were included in the control group, and those with moderate-severe OSAS were included in the patient group. No statistically significant difference was found between the control group and the patient group regarding age, phosphorus, calcium, serum Vitamin D, and serum PTH levels. In some OSAS diseases, vitamin D levels are not low. In our study, age was higher and smoking was found to be higher with BMI in the severe OSAS group. The lowest Vitamin D level was found in the severe OSAS group. However, Çelikhiisar et al. As it is, there was no significant difference in PTH levels. Variables such as occupation, age, physical activity, gender, weight can produce different results in the relationship between OSAS and vitamin D. It is known that acceleration, brake movements and stop-and-go movements are quite frequent in urban traffic due to heavy traffic and traffic lights. Therefore, hip, leg, and arm activity is quite high. This type of physical activity is equivalent to regular exercise, which can cause normal vitamin D values and not detecting high PTH levels, such as in those who exercise regularly [3].

Vitamin D and PTH, except for bone and Ca metabolism is also associated with obesity, DM, MS, and insulin resistance (IR) [14]. Vitamin D treatment decreases systemic inflammation by decreasing insulin resistance [15]. Vitamin D deficiency and PTH elevations in patients with OSAS are associated with abnormal glucose metabolism. Zegin Fan et al. found that IR in the severe OSAS group was significantly higher than in the control group. Vitamin D values are negatively correlated with AHI and IR [16]. We did not measure IR, because the study was retrospective and this was not our aim. But we eliminated those with comorbid disease detectable by background reports at the beginning of the study.

OSAS is a disease that progresses with complete or partial obstruction of the upper respiratory tract and causes hypoxia and sleep interruption. Continuous positive airway pressure (CPAP) therapy is the best treatment method today. Claudio et al. found that after seven nights of CPAP treatment, vitamin D levels of male patients who responded to treatment were significantly higher than before the CPAP treatment. They could not find the same increase in female patients who responded to the treatment. This study concluded that short-term CPAP therapy increased vitamin D levels in male patients. OSAS often affects women after menopause. The same effect may not be seen in women because postmenopausal hormones are important in vitamin D regulation. In the future, more studies are needed to investigate the positive effects of CPAP treatment on vitamin D and PTH levels [17].

Salepci et al. concluded that there was no difference between the vitamin D levels of patients with and without OSAS. They also found no relationship between vitamin D levels and diabetes, age, ODI, and min SO2 [18]. This may be because the study groups were small, it was a cross-sectional study, and many factors affect vitamin D levels. Some studies of populations in developing countries, including Turkey, reported having low levels of vitamin D [19]. Forty-seven percent of the population in a population-based study conducted in Turkey had vitamin D deficiency with an average vitamin D level of 22.8ng/mL [20]. In our study, vitamin D levels are lower than the general population in Turkey because we measured the level of vitamin D in patients undergoing PSG.

Barcela et al. divided patients with OSAS into three groups according to their vitamin D levels as normal, low and very low. Patients with very low vitamin D levels have higher AHI, arousal index, glucose, cholesterol, triglyceride, and PTH levels, and minSO2, and mean SO2 values are lower in older patients [21]. In our study, we grouped the patients according to AHI level, not Vitamin D level. We found the highest total cholesterol, triglyceride, and LDL values in the severe OSAS group, the group with the lowest vitamin D levels in the severe OSAS group.

There are different hypotheses to explain the relationship between OSAS and vitamin D. Pro-inflammatory cytokines increase in vitamin D deficiency, and anti-inflammatory cytokines decrease. Thus, with the increase of inflammatory pathways, vitamin D deficiency may cause OSAS [22]. Also, as in chronic obstructive pulmonary disease (COPD), hypoxia may be the cause of vitamin D deficiency in patients with OSAS [23]. Another important issue is inadequate vitamin D levels; adenotonsillar hypertrophy may increase the risk of OSAS by causing chronic rhinitis and upper respiratory muscle myopathy [24]. Limited exposure to sunlight due to excessive daytime sleepiness, restricted physical activity due to obesity, and inadequate nutrition are causes of vitamin D deficiency [25]. The ages, sexes and BMIs of the patient and control groups were matched in the study by Ahmed Abbas et al. The Epworth Sleepiness Scale (ESS) was applied to both groups, but PSG was not used with the control group. When the patients with OSAS were compared with the control group, ESS was higher and vitamin D values were lower. Vitamin D values are low in patients with OSAS and this correlates with the severity of the disease [26]. In the future, multi-center cross-sectional, prospective studies are needed to examine the effects of vitamin D treatment on disease severity and quality of life in patients with OSAS.

Some studies have shown that there are vitamin D receptors (VDR) in neuronal and glial tissues in the central nervous system, as in all tissues in the body [27]. VDRs are present in many regions of the human brain such as the prefrontal cortex, cingulate gyrus, thalamus, substantia nigra, and hippocampus, including the hypothalamus, a brain region that regulates the sleep-wake cycle [28]. Obstructive sleep apnea and short sleep duration are associated with low serum vitamin D levels. The greater proportion of sleep symptoms and disturbances in older adults may support that an age-related mechanism related to vitamin D affects serum levels and metabolism. Vitamin D deficiency is increasingly common in both OSA and sleep shortening, and is thought to be linked to the most common chronic diseases. In the study of Ronaldo et al. short sleep duration was evaluated as total sleep time <6 hours and Vitamin D deficiency <30 ng/mL. In their study, they concluded that age, sex, ethnicity, obesity, smoking, hypertension, diabetes, sedentary lifestyle, seasonality, and creatinine serum levels were associated with vitamin D deficiency in both OSAS and short sleep. To our knowledge, their study is the first to show that moderate to severe OSAS and short sleep duration are associated with vitamin D deficiency [29].

Vitamin D is one of the most important factors in hypoxia, reoxygenation attacks and cytokine release mechanism in OSAS [30]. It has been shown in many studies, that systemic biomarkers such as interleukin (IL)-6, C-reactive protein (CRP) and IL-17 increase in OSAS [31,32]. Redline et al. also found that IL-17 increased in OSAS and was related to the severity of OSAS [33]. To better understand the mechanisms of serum vitamin D deficiency and its relationship with inflammation in patients with OSAS, future multicenter clinical studies are needed.

OSAS is generally seen in a population with common obesity and is associated with endocrine pathologies such as T2DM [34-36]. Danyan et al. reported that serum vitamin D levels had no significant relationship with AHI; however, they stated that it increased the risk of OSAS in patients with T2DM [37]. The fact that most patients with T2DM patients were obese, the study being cross-sectional, and having a limited number of patients may have been the limitations of this study.

In a meta-analysis performed by Sikarin et al., it was stated that moderate and severe OSAS were associated with low vitamin D levels [38]. The low vitamin D level in OSAS is due to hypoxia caused by chronic obstructive pulmonary disease (COPD). This was the first systemic review and meta-analysis to investigate the relationship between OSAS and low vitamin D levels. There were no chronic diseases such as COPD in our patient population.

The limitations of our study include the effects of many diseases on vitamin D levels, the possibility of vitamin D supplementation even if there is no such record in the hospital data, and the fact that vitamin D levels can be affected by seasonal conditions and nutritional status.

Conclusions

Vitamin D deficiency is observed in patients with OSAS and is related to the severity of the disease. In the follow-up of patients with OSAS and compliance with treatment, instead of an expensive and time-consuming procedure like PSG, we can look at vitamin D levels in the outpatient clinic. We think that vitamin D therapy may be beneficial in reducing the severity of the disease.

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The roles of fasting blood glucose to HDL-cholesterol ratio and monocyte to HDL-cholesterol ratio on coronary slow flow in non-diabetic patients

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Abstract

Aim: This study aimed to evaluate the relationship between coronary slow flow (CSF) with fasting blood glucose/high-density lipoprotein cholesterol ratio (GHR) and monocyte/high-density lipoprotein cholesterol ratio (MHR) in patients without overt diabetes and to reveal the effects of hyperglycemia and inflammation on CSF development.

Material and methods: In this retrospective study, a total of 237 patients who underwent coronary angiography were enrolled and were divided into two groups according to CSF presence. 109 of them had CSF and 128 of them had coronary normal flow (CNF). The thrombolysis in myocardial infarction (TIMI) frame count (TFC) was calculated for each coronary artery and the values above the normal range were defined as CSF.

Results: GHR and MHR were significantly higher in CSF patients compared to those without ($p<0.001$, $p<0.001$). In correlation analysis, total TFC showed a statistically significant relation with these markers (for both $r=0.745$, $p<0.001$). In multivariate logistic regression analysis, GHR and MHR were independent predictors for CSF presence ($p<0.001$, $p<0.001$). The receiver operating characteristic (ROC) curve analysis showed the best cut off values of GHR and MHR as 2.105 and as 12.93, respectively (AUC=0.861, $p<0.001$; AUC=0.849, $p<0.001$).

Conclusion: In this study, there was a strong relationship between CSF with GHR and MHR. In addition, elevated values of GHR and MHR supported the roles of hyperglycemia and inflammation in CSF etiopathogenesis.

Key words: coronary slow flow, fasting blood glucose, high-density lipoprotein cholesterol, monocyte counts

Introduction

Coronary slow flow (CSF) is characterized by delayed perfusion of distal vessels in the absence of significant epicardial coronary stenosis [1]. Although the underlying etiopathogenic mechanisms have been the focus of many researchers for years, these mechanisms are still not clearly understood. It has been proposed that microvascular disorders, endothelial dysfunction, systemic inflammation, blood cell abnormalities, and occult atherosclerosis may play a role in the pathogenesis [2].

Diabetes is a well-known risk factor for coronary artery disease (CAD) and there is growing evidence on the relationship between fasting blood glucose (FBG) and microvascular complications. However its effect on macrovascular complications such as CAD is relatively less clear [3-5]. While it has been debated whether elevated FBG levels may be a risk factor for CAD in non-diabetic patients, some studies have revealed that hyperglycemia has negative effects on CAD in this population [6,7]. As with CAD, few studies reported the association of

CSF considered as early stage of CAD with hyperglycemic conditions other than diabetes. Hence, it has been assumed that hyperglycemic states such as insulin resistance (IR) may impair the coronary microvascular circulation due to endothelial damage before overt diabetes manifests [8,9]. However, more data are needed to support the effects of hyperglycemia on CSF.

Dyslipidemia, like diabetes, is a traditional cardiovascular risk factor and related to adverse cardiovascular outcomes [10]. The previous studies demonstrated the relationship between CSF with high-density lipoprotein cholesterol (HDL-C) and triglyceride levels [11,12]. Recently, as a novel marker, the FBG/HDL-C ratio (GHR) has been reported as an independent predictor for all-cause mortality in non-diabetic patients undergoing percutaneous coronary intervention (PCI) [13]. To our best knowledge, the role of this novel marker in non-diabetic patients has not yet been investigated.

Monocyte count to HDL-C ratio (MHR) is a marker associated with inflammation and the studies have reported that MHR may predict cardiovascular disease (CVD), stent thrombosis and adverse cardiovascular outcomes [14-16]. However there are few data on the relationship between MHR and CSF [17]. Thus, in this study, we aimed to evaluate the effect of hyperglycemia and inflammation on CSF etiopathogenesis using GHR and MHR.

Material and methods

Patients and clinical data

In this single-center study, a total of 237 patients, including 128 coronary normal flow (CNF) and 109 coronary slow flow (CSF) patients who applied to our cardiology outpatient clinic with stable angina and/or equivalent symptoms and underwent coronary angiography for suspected CAD, were retrospectively analyzed. The patients with a history of CAD or revascularization, left ventricular dysfunction (ejection fraction<50%), congenital heart disease, overt diabetes, cerebrovascular disease, malignancy, acute or chronic inflammation, autoimmune disorders, severe kidney or liver disease were excluded. In addition, patients receiving drugs that affect glycolipid metabolism were also excluded from the study.

The clinical, laboratory and angiographic data of each patient were obtained from the hospital registry system. From fasting blood, GHR was calculated by dividing the glucose level by the HDL-C level, and MHR was calculated by dividing the monocyte cell count by the HDL-C level. The study was approved by the Ethics Committee of the Pamukkale University, Faculty of Medicine in accordance with the Helsinki declaration (protocol No E-60116787-020-56171).

Coronary angiography

The recorded views on the digital system were examined by two experienced cardiologists who were blind to the clinical data of the study population. The thrombolysis in myocardial infarction (TIMI) frame count (TFC) was calculated as described by Gibson et al. [18]. TFC was obtained by calculating the difference between the frame where the contrast enters the coronary artery and the last frame where the contrast reaches the distal coronary landmark. The distal bifurcation for left anterior descending artery (LAD), the distal bifurcation of the longest branch for left circumflex artery (LCx), and the first side branch of the posterolateral artery for right coronary artery (RCA) were defined as the distal ends. The normal range of CNF was accepted for LAD as a 36.2±2.6 frames, for LCx as a 22.2±4.1 frames and for RCA as a '20.4±3.0' as previously defined by Gibson et al. [18]. The greater than 2 standard deviations from these thresholds were considered CSF. The cine frames were recorded at a 15 frames/second in this study so the values were multiplied by 2. Since, LAD was longer, the frame count was divided by 1.7 to calculate the corrected TFC.

Statistical analysis

All data were analyzed using SPSS version 21.0 software (SPSS, Inc., Chicago, Ill., USA). The normality of the distribution was checked using Kolmogorov-Smirnov test. Continuous and categorical variables were presented as the mean ± standard deviation (SD) and as the number (percentage). In comparison of continuous variables, the independent-sample t test or Mann–Whitney U test was used. The Chi-squared test was performed to compare the categorical variables. The variables with significant relationship ($p<0.05$) in univariate analysis, which were considered to be risk factors for CSF and did not show multicollinearity, were included in multivariate logistic regression analysis. GHR and MHR were taken place in different regression models due to the multicollinearity. The relation between total TFC with GHR and MHR was revealed using the Spearman correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive power of GHR and MHR for CSF presence. In determining the best cut off values of these parameters, the Youden Index, which overlaps with the point closest to the upper left corner of the ROC curve graph and reflects the value with the highest sum of sensitivity and specificity, was used. A 2-sided p value of <0.05 was considered significant.

Results

This study was conducted with a total of 237 patients. The mean age of the whole population was 56.84±11.42 years and the male sex ratio was 60.8%. The demographic and clinical data of the patients according to having CSF are summarized in Table 1. There was no significant difference in demographical data such as smoking, hypertension and hyperlipidemia between the groups. CSF patients showed significantly higher levels of white blood cells (WBC), monocytes, FBG, glycated hemoglobin (HbA1c), creatinine, triglycerides (TG), C-reactive protein (CRP) and significantly lower levels of HDL-C. However, ejection fraction, hemoglobin, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were similar. The total TFC was higher in CSF patients compared to CNF patients as expected (93.04±17.56 vs 54.90±6.91, $p<0.001$). Of the CSF, 73.4 % was associated with the LAD artery, 50.5% with the LCx artery, 66.1% with the RCA. In addition 43 patients (39.4%) had CSF in a single vessel and 66 patients (60.6%) had CSF in two or three vessels on angiographical views. GHR was calculated as 2.61±0.47 and 1.84±0.54 in patients with and without CSF, respectively, and there was a strong statistical significance ($p<0.001$). MHR was significantly higher in CSF patients compared to those without (18.33±7.34 vs 10.61±3.83, $p<0.001$) (Table 1, Figure 1).

Total TFC was significantly associated with GHR and MHR in correlation analysis (for both $r=0.745$, $p<0.001$) (Figure 2). Then GHR and MHR were evaluated in terms of whether that they may be independent markers for CSF presence using multivariate logistic regression analysis. However two models were performed in regression analysis because of multicollinearity. In model 1, MHR ($p<0.001$), HbA1c ($p<0.001$) and CRP ($p=0.023$) were identified as independent predictors for CSF presence. In model 2, only GHR was an independent

Table 1 Baseline characteristics and clinical data of the study population

Variables	All population (n=237)	CNF group (n=128)	CSF group (n=109)	p-value
Demographics				
Age (years)	56.84±11.42	57.34±10.57	56.25±12.37	0.308
Male gender, n (%)	144 (60.8)	75 (58.6)	69 (63.3)	0.459
Hypertension, n (%)	123 (51.9)	67 (52.3)	56 (51.4)	0.882
Hyperlipidemia, n (%)	44 (18.6)	23 (18)	21 (19.3)	0.798
Smoking, n (%)	85 (35.9)	44 (34.4)	41(37.6)	0.604
Ejection fraction (%)	58.66±3.51	58.98±3.15	58.28±3.88	0.108
Laboratory				
Hemoglobin, g/ dL	14.34±6.94	14.07±1.40	14.66±10.14	0.115
WBC, $10^3/\mu L$	9.12±5.12	8.08±1.81	10.35±6.96	<0.001
Monocyte, ($10^9/L$)	567.93±190.90	477.03±97	674.68±217.43	<0.001
FBG, mg/dL	90.34±11.75	83.98±9.43	97.81±9.64	<0.001
HbA1c (%)	5.63±0.54	5.33±0.45	5.99±0.40	<0.001
Creatinine, mg/dL	0.82±0.15	0.78±0.13	0.85±0.16	<0.001
Tchol, mg/dL	187.76±39.88	186.62±41.90	189.09±37.51	0.635
TG, mg/dL	158.22±63.52	132.21±55.98	188.75±58.20	<0.001
LDL-C, mg/dL	111.88±34.36	112.70±33.73	110.92±35.22	0.691
HDL-C, mg/dL	43.56±10.22	48.05±10.80	38.28±6.23	<0.001
CRP, mg/dL	0.64±0.56	0.43±0.28	0.89±0.69	<0.001
GHR	2.19±0.63	1.84±0.54	2.61±0.47	<0.001
MHR	14.16±6.88	10.61±3.83	18.33±7.34	<0.001
Corrected TIMI frame count				
LAD	25.22±9.02	19.31±2.08	32.17±9.08	<0.001
Lcx	23.07±8.46	17.89±3.58	29.16±8.50	<0.001
RCA	24.03±9.26	17.78±3.37	31.36±8.57	<0.001
Total TFC	72.44±23.02	54.90±6.91	93.04±17.56	<0.001
Slow flow related artery				
LAD, n (%)	80 (73.4)	-	80 (73.4)	-
Lcx, n (%)	55 (50.5)	-	55 (50.5)	-
RCA, n (%)	72 (66.1)	-	72 (66.1)	-
Single vessel, n (%)	43 (39.4)	-	43 (39.4)	-
Multi vessel, n (%)	66 (60.6)	-	66 (60.6)	-
Medications				
RAS blocker, n (%)	89 (37.6)	49 (38.3)	40 (36.7)	0.802
CCB, n (%)	45 (19)	29 (22.7)	16 (14.7)	0.119
Diuretics, n (%)	28 (11.8)	10 (7.8)	18 (16.5)	0.039
Statin, n (%)	32 (13.5)	18 (14.1)	14 (12.8)	0.784

CNF- coronary normal flow; CSF- coronary slow flow; FBG- fasting blood glucose; TG- triglycerides; Tchol- total cholesterol; LDL-C- low-density lipoprotein cholesterol; HDL-C- high-density, lipoprotein cholesterol; WBC- white blood cells; CRP- C-reactive protein; LAD- left anterior descending artery; LCx- left circumflex artery; RCA- right coronary artery; TIMI- thrombolysis in myocardial infarction; TFC- "thrombolysis in myocardial infarction" frame count; RAS- Renin-angiotensin system; CCB- calcium channel blockers; GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio

Figure 1a - The comparison of GHR values between the groups

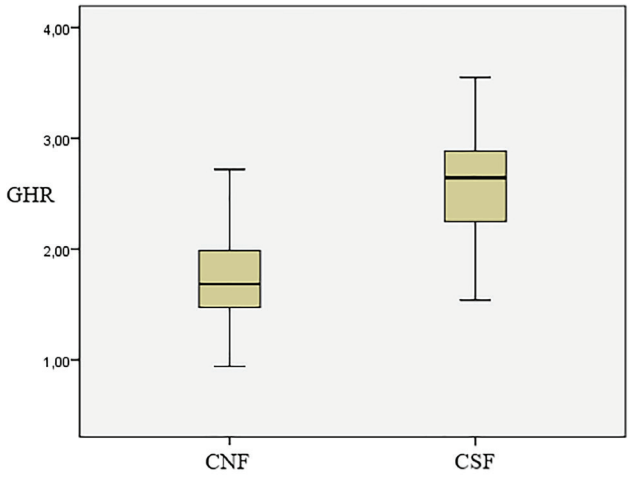
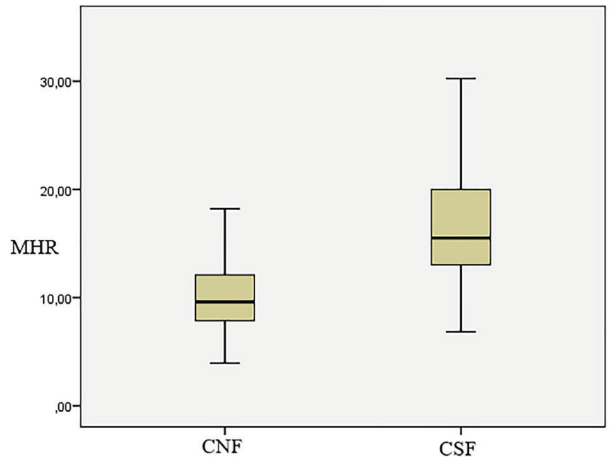


Figure 1b - The comparison of MHR values between the groups



Abbreviations: GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio; CNF- coronary normal flow; CSF- coronary slow flow

Figure 2a - The relationship between total TFC and GHR

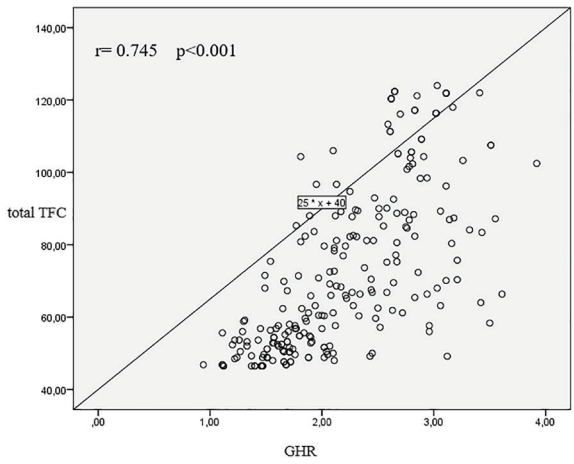
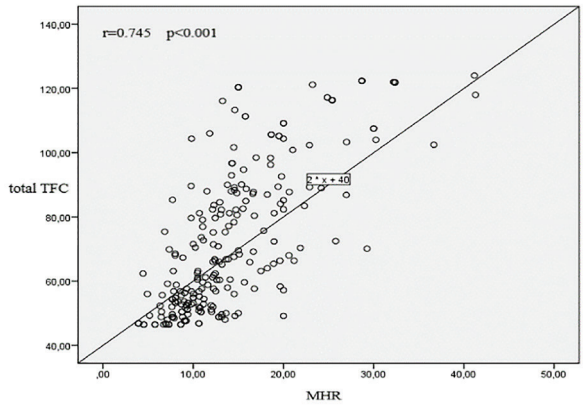


Figure 2b - The relationship between total TFC and MHR



Abbreviations: TFC- "thrombolysis in myocardial infarction" frame count; GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio

Table 2 The multiple logistic regression analysis in predicting of CSF presence

Model 1

Variables	OR	95% CI	p-value
WBC	1.059	0.972-1.154	0.192
HbA1c	15.804	6.144-40.601	<0.001
Creatinine	0.096	0.006-1.577	0.101
CRP	0.263	0.083-0.831	0.023
MHR	1.320	1.184-1.471	<0.001
Constant	.000	-	<0.001

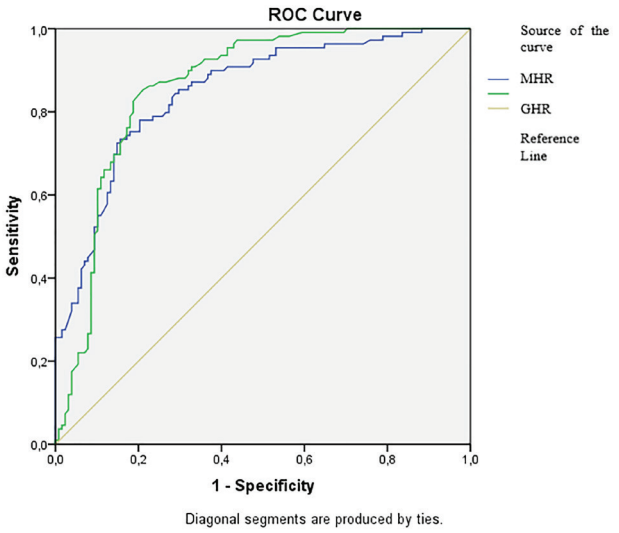
CSF- coronary slow flow; WBC- white blood cells; CRP- C-reactive protein; MHR- monocyte to HDL-C

Model 2

Variables (Model 2)	OR	95% CI	p-value
WBC	1.144	0.970-1.350	0.109
TG	1.003	0.995-1.010	0.485
Creatinine	0.732	0.061-8.774	0.805
CRP	0.733	0.573-4.149	0.392
GHR	8.773	3.906-19.704	<0.001
Constant	0.001	-	<0.001

CSF- coronary slow flow; WBC- white blood cells; TG- triglycerides; CRP- C-reactive protein GHR- glucose to HDL-C ratio

Figure 3 - The receiver–operator characteristic (ROC) curve to determine the best cut-off values of GHR and MHR in predicting of CSF presence



Abbreviations: CSF- coronary slow flow; GHR- glucose to HDL-C ratio; MHR- monocyte to HDL-C ratio

predictor for CSF presence (p<0.001) (Table 2). The receiver operating characteristic (ROC) curve analysis showed the GHR and MHR best cut off values as 2.105 at 78.91% specificity and 85.32% sensitivity, and as 12.93 at 79.69% specificity and 77.98% sensitivity, respectively (GHR, AUC=0.861, 95% CI=0.813-0.910, p<0.001; MHR, AUC=0.849, 95% CI=0.800-0.898, p<0.001) (Figure 3).

Discussion

In this study, we eveluated the relationship of CSF with GHR and MHR and revealed that these markers were increased in CSF presence regardless of all-causes. In addition, these markers were strongly correlated with total TFC, which indicates CSF severity.

CSF is an angiographic entity detected at a rate of 1-7% in patients with suspected CAD. It should be recognized without delay due to risk of hypotension, acute coronary syndrome, life-threatening arrhythmia and sudden death [19,1]. Although the etiopathogenesis of CSF remains unclear, there is increasing data suggesting the role of hyperglycemia and inflammation in this process. Elevated FBG levels are often related to IR and trigger oxidative stress, protein C kinase activation and non enzymatic protein glycosylation, resulting in acceleration of atherosclerosis by impairment of endothelial cell function, the decrease of NO release and inducing of procoagulant [20,21]. Several studies have demonstrated that increased FBG may lead to an increase risk of cardiovascular risk factors and CAD [22,23]. As in CAD, hyperglycemia may be responsible for CSF pathogenesis due to its adverse effects on endothelial function. Indeed, some data have confirmed this relation by showing the impairment of flow-mediated dilatation in the brachial artery and the decrease of endothelin-1, NO, homocysteine and diethyl methyl arginine responsible for vasomotor tonus [1]. Moreover, endothelial dysfunction may be accepted as an early stage of atherosclerosis, and a higher TFC may reflect the microvascular resistance of coronary arteries [24,25]. One study demonstrated that the impairment glucose tolerance was common in patients with CSF even if absence of overt diabetes and another study revealed the

effects of hyperglycemia on non-diabetic CSF patients [26,27]. Moreover Ozan et al. [28] and Arslan et al. [29] found a higher TFC in patients with IR compared to those without.

HDL-C is one of the lipid parameter related to CAD and mortality independently from other cardiovascular risk factors. It is also known that HDL-C particles protect the endothelial cells by preventing LDL-C oxidation [30]. Lower HDL-C levels were found to be an independent predictor for CSF in some studies and Sezgin et al. reported that low HDL-C levels may play a role in endotelial dysfunction in CSF [11,12]. However, Kalayci et al. [31] failed to show the relationship between CSF with HDL-C and attributed these contradictory findings to smoking, insufficient exercise time, and use of lipid-lowering drugs. GHR is a novel marker derived from the FBG and HDL-C, and one study showed that GHR may be an independent predictor for adverse cardiovascular outcomes in non-diabetic patients [13]. GHR may be considered as a marker indicating IR. Because IR is not only associated with hyperglycemia but also the impairment of lipid metabolism including elevated of triglycerides and LDL-C levels, and lower of HDL-C levels [32]. For the first time, we investigated the relationship between GHR with CSF in this study. We showed that GHR was elevated in non-diabetic CSF patients and was an independent predictor for CSF presence. We also confirmed that, as in previous studies, IR may play a role in CSF pathogenesis [24-29]. Furthermore, Yılmaz et al. [33] found a higher prevalence of metabolic syndrome associated with impairment of glycolipid metabolism in CSF patients. Another finding of our study was higher levels of HbA1c in CSF patients, similar to previous studies [34,35]. However some data have reported that CSF may not be related to hyperglycemia [36]. The inconsistencies between the studies may be linked to size of the sample, the characteristics of study population, inclusion and exclusion criteria, measurement technique differences, and drug use.

Monocytes and macrophages are blood cells associated with immunity, and circulating monocytes migrate to atherosclerotic plaques, differentiate into macrophages, and contribute to atherosclerosis by forming foam cells [37]. On the other hand, HDL-C particles exert an anti-atherosclerotic and anti-inflammatory effects by inhibiting macrophage migration, activation and adhesion [38]. MHR is a novel marker for inflammation and several studies have shown its relationship with CAD and adverse cardiovascular outcomes [16,14]. However, the role of MHR in CSF pathogenesis is not clearly elucidated. Canpolat et al. [17] published a study that MHR may be an independent predictor of CSF presence and supported our findings. Another remarkable point in our study was the higher CRP levels in patients with CSF. Previous studies found a relationship between elevated CRP levels and CSF. In addition, it has been suggested that CSF is not only localized coronary artery pathology but also a systemic vascular disorder in which many local and systemic inflammatory factors contribute to its development [39,17,1].

Our study had some limitations. First, the study was a single-center study and had a relatively small sample. Due to a more homogeneous sample, the study findings cannot be generalized to the whole population and different ethnic groups. In addition, we cannot ignore the potential risk of bias and relative overestimation in single-center studies. Second, we measured FBG, HDL-C levels and monocyte cell counts only once at admission. Therefore, we may not exclude possible laboratory errors. Third, in the evaluation of endothelial dysfunction, we did not use advanced methods such as intravascular ultrasound or computed tomography, that present more reliable information on atherosclerosis.

Conclusion

As a result, in this study, we confirmed that both hyperglycemia and inflammation play a role in CSF etiopathogenesis by demonstrating elevated GHR and MHR in CSF, independent from all-causes. Our findings also provide a new evidence that endothelial dysfunction may develop without overt diabetes manifests. However, our findings need to be confirmed by larger-scale prospective studies.

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Comparison of spinal versus caudal epidural anesthesia in the management of patients undergoing ambulatory perianal surgery: Randomized, prospective study

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Abstract

Objective: To compare levobupivacaine based caudal epidural anesthesia and spinal anesthesia in terms of Intraoperative hemodynamic changes and postoperative pain and patients' satisfaction in subjects undergoing perianal surgery in outpatient setting.

Material and methods: All consecutive patients who were scheduled for perianal surgery. The difference in intraoperative hemodynamic changes, sensory and motor block level, postoperative pain and patients' satisfaction was the primary outcome measure of this study.

Results: There were no significant differences between the groups in terms of mean arterial pressure and heart rate recorded. Subjects randomized to spinal anesthesia had a significant extensive motor and sensory block compared to those randomized to caudal epidural anesthesia. Visual analogue scale (VAS) scores for surgical pain at postoperative 12 hours was significantly higher in subjects receiving spinal anesthesia compared to those receiving caudal epidural anesthesia (p=0.012). Time to first analgesic administration was significantly lower in subjects randomized to spinal anesthesia compared to those receiving caudal epidural anesthesia (p=0.011).

Conclusion: Spinal anesthesia is associated with more extensive sensory and motor block compared to caudal epidural anesthesia in patients undergoing perianal surgery. Both techniques lead to similar hemodynamic changes. Postoperative pain control is more favorable with caudal block than the spinal anesthesia.

Key words: spinal anesthesia, perianal surgery, caudal anesthesia, analgesia

Introduction

Advances in anesthetic and surgical techniques led to an increase in outpatient surgical procedures. Performing several surgeries in outpatient setting not only reduces healthcare costs but also increases patients' satisfaction due to same day discharge after the procedure [1]. Regional intravenous anesthesia, spinal and epidural block, peripheral nerve block, topical and local anesthesia are commonly utilized in anesthesia of outpatient surgical procedures [2-5].

Perianal surgery which can be performed in outpatient setting is often performed for perianal abscess, perianal fistula, hemorrhoids, and anal fissures. General anesthesia, local anesthesia, and regional anesthesia techniques have traditionally been used in anesthesia management of patients undergoing perianal surgery [6,7]. General anesthesia has been reported to prolong hospital stay and patient discharge as a consequence of postoperative nausea and vomiting and postoperative pain compared to local and regional anesthesia [8,9]. On the other hand, perianal surgery with local anesthetic infiltration requires concomitant sedation which can reduce patient comfort [10-12]. Regional anesthetic techniques might be unique for use in perianal surgery since spontaneous breathing is prevented, preventative reflexes remained active, and subjects are often mobilized in early postoperative period.

Spinal anesthesia or regional caudal block may be used for the anesthetic management of the perianal surgery. Spinal anesthesia is a simple anesthetic technique which can provide adequate muscle relaxation and analgesia with low dose local anesthetic agents [13,14]. However, spinal anesthesia might be insufficient, particularly in prolonged surgical procedures and additional analgesic management may be required for postoperative pain [15-17]. Caudal epidural anesthesia is safely used in anesthetic management of patients undergoing hemorrhoid surgery. Advantages of caudal epidural anesthesia over spinal anesthesia include segmental block, and limited motor block which enables early mobilization [18-20]. However, data comparing the intra-and postoperative effects of caudal epidural anesthesia and spinal anesthesia in outpatient setting is limited.

This study aimed to compare levobupivacaine based caudal epidural anesthesia and spinal anesthesia in terms of intraoperative hemodynamic changes and postoperative pain and patients' satisfaction in subjects undergoing perianal surgery in outpatient setting.

Material and methods

After the local ethic committee approval 70 patients aged ≥ 18 years, and were American Society of Anesthesiologists (ASA) class I-II, who were scheduled for perianal surgery for perianal abscess, perianal fistula, hemorrhoids, and anal fissures were included in this study. Those with vertebral colon deformities, neurological or hematological disorders, and obese patients (body mass index > 30 kg/m2) and subjects with known allergy to levobupivacaine were excluded.

Before randomization, all eligible subjects received standardized verbal and written information from a research fellow. Written informed consent was obtained from all subjects. Subjects were randomly assigned to caudal epidural anesthesia (Group C, n=35) or spinal anesthesia (Group S, n=35) using random allocation software. Sealed envelopes indicating patients' group were opened at operation theatre. Heart rate and peripheral oxygen saturation (SpO2) were monitored continuously; systolic, diastolic, and mean arterial pressure (MAP) were measured noninvasively at 5 min intervals during the procedure. The baseline values were recorded. All subjects received 2 L/min of nasal oxygen was during the whole procedure. A > 30 % decrease in MAP from the baseline measurement or a drop in systolic blood pressure < 90 mmHg was defined as hypotension. 5-10 mg intravenous ephedrine was administered in case of Intraoperative hypotension. Heart rate < 50 beats/min was defined as bradycardia. 0.5 mg intravenous atropine was administered to manage intraoperative bradycardia.

All patients were received 1-2 mg of midazolam and 25-50 µg of fentanyl intravenously for premedication before the procedure. Spinal anaesthesia was performed at the L3-4 or L4-5 intervertebral space with the patient in the left-lateral decubitis position with a midline approach and a 25 G (gauge) needle. After confirmation of free flow of clear cerebrospinal fluid, 2.5ml of 0.5% levobupivacaine + 25 µg fentanyl was injected into the intrathecal space in 15 seconds. Caudal epidural anesthesia was performed at sacral hiatus with the patient in the prone position with a 18 G (gauge) tuohy needle. 0.25 ml/kg of 0.5% levobupivacaine with 25 µg fentanyl was then injected into the epidural space to achieve adequate anesthesia. Patients were then taken to supine position with the head elevated to 30 degrees. The sensorial block was measured at the midclavicular line with a pinprick test and the motor block was measured using the modified Bromage scale (0: no motor block, 1: hip blocked, 2: hip and knee blocked, and 3: hip, knee, and ankle blocked). Onset time and maximum cephalad spread of sensory block were recorded. All surgical procedures were carried out by the same surgical team.

Heart rate, MAP, motor block, and sensorial block, were recorded preoperatively and at 5 minutes intervals intraoperatively, and after completion of the surgery. Surgical pain was evaluated through a visual analogue scale (VAS) score (0 indicating no pain and 10 indicating the worst pain experienced ever). In postoperative period, subjects with a VAS score of ≥ 5 received 50 mg intravenous tramadol, and time to first analgesic administration was recorded. Surgeons' and patients' satisfaction was evaluated by a 4 points Likerts scale postoperatively (1 indicating low satisfaction, 2 indicating moderate satisfaction, 3 indicating good satisfaction, and 4 indicating perfect satisfaction).

The difference in intraoperative hemodynamic changes, sensory and motor block level, postoperative pain and patients' satisfaction was the primary outcome measure of this study.

Statistical analysis

Statistical analyses were carried out using SPSS (Statistical Package for the Social Sciences) for Windows, version 17 (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.). Normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation (mean ± SD) and categorical variables as frequency (n) and percentage (%). The comparison of the two groups was performed with Student's t-test, Mann–Whitney U-test, $\chi 2$ -test or Fisher's exact test, where appropriate. Two-sided p-value < 0.05 was interpreted as statistically significant.

Results

Twelve patients who did not meet the inclusion criteria were excluded, and total of 58 patients were studied as caudal epidural anesthesia (n=28) or spinal anesthesia (n=30). The two groups were similar with respect to age (p=0.183), gender (p=0.085), body mass index (p=0.137), operation time (p=0.59) and ASA risk score (p=0.369). Onset time of sensory block in Group S (4.6±3.8) was faster than Group C (13.5±5.4) (p=0.017) (Table 1).

Table 1 Patients' General Characteristics and Intraoperative Data (mean ± Sd)

	Group C (n=28)	Group S (n=30)	P - value
Age (years)	46±12	41±14	p= 0.183
Gender(male/ female)	21/7	20/10	p = 0.085
BMI (kg/m2)	27.63 ± 3.76	25.92 ± 3.47	p= 0.137
ASA risk score (n) I/II	17/11	19/11	p= 0.369
Operation time (min)	26.94 ± 15.24	29.63 ± 16.69	p= 0.59
Onset time of sensory block	13.5 ± 5.4	4.6 ± 3.8	p=0.017*

*p<0.05: Onset time of sensory block in Group S was faster than Group C

There were no significant differences between the groups in terms of MAP and heart rate recorded pre-intra-and postoperatively (Table 2). Significant differences were observed between the groups in terms of motor block. Intense motor block was seen in the spinal anesthesia group, whereas no motor

Table 2 Mean arterial pressure and heart rate of the groups (Mean±SD)

	Group C (n=28)	Group S (n=30)	p-value
Mean arterial pressure (mmHg)			
Preoperative	93.72±13.53	101.71±17.86	p=0.059
Post-caudal/spinal 5th min	89.50±15.51	95.71±15.84	p=0.248
10th min	90.67±11.42	94.88±14.60	p=0.488
15th min	91.94±13.29	91.13±15.59	p=0.813
30th min	94.67±12.29	88.75±14.59	p=0.747
Post-surgery 1st min	93.01±0.29	91.05±17.50	p=0.388
Postoperatif 15th min	89.45±11.27	87.57±12.56	p=0.897
Heart rate (beats/min)			
Preoperative	78.17±12.53	85.42±18.75	p=0.060
Post-caudal/spinal 5th min	73.33±9.95	79.29±19.22	p=0.201
10th min	73.56±14.16	78.88±16.72	p=0.283
15th min	72.83±13.12	78.04± 17.00	p=0.287
30th min	70.44±11.19	77.92±16.77	p=0.110
Post-surgery 1st min	69.13±8.89	75.55±18.32	p=0.179
Postoperatif 15th min	66.30±4.54	74.21± 14.44	p=0.072

Table 3 Modified Bromage scores of the study groups

	Group C		Group S		p-value
	n=28	%	n=30	%	
Post-caudal/spinal 5th min					
0	28	100	6	20	p=0.002*
1	0	0	8	26.6	
2	0	0	7	23.3	
3	0	0	8	26.6	
Post-caudal/spinal 10th min					
0	28	100	4	13.3	p=0.001*
1	0	0	5	16.6	
2	0	0	8	26.6	
3	0	0	13	43.3	
Post-caudal/spinal 15th min					
0	28	100	3	10	p=0.001*
1	0	0	4	13.3	
2	0	0	6	20	
3	0	0	17	56.6	
Post-caudal/spinal 30th min					
0	28	100	3	10	p=0.001*
1	0	0	4	13.3	
2	0	0	6	20	
3	0	0	17	56.6	
Completion of the surgery					
0	28	100	3	10	p=0.001*
1	0	0	4	13.3	
2	0	0	8	30	
3	0	0	15	43.3	
Postoperative 15th min.					
0	28	0	3	10	p=0.001*
1	0	0	5	16.6	
2	0	0	10	33.3	
3	0	0	12	40	

block was seen in the caudal epidural anesthesia group (Table 3). Maximum sensory blocks reached T6 dermatomes in spinal anesthesia group and T10 in caudal epidural group. Subjects randomized to spinal anesthesia also had a significantly more extensive sensorial block compared to those receiving caudal epidural anesthesia (Figure 1).

Figure 1 - Comparison of the groups with respect to the level of sensory block

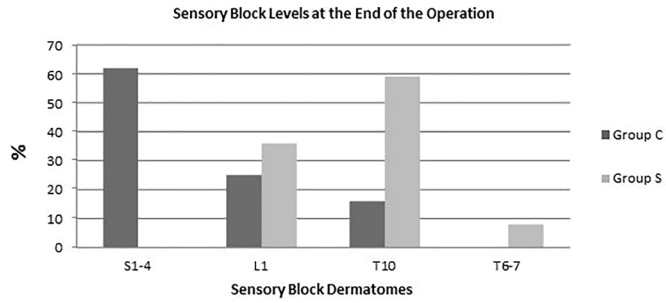

Table 4 Postoperative visual analogue scale (VAS) (Mean±SD)

	Group C (n=28)	Group S (n=30)	p-value
Postoperative 15th min	1.56 ± 0.126	1.78 ± 0.18	p=0.084
Postoperative 2nd hour	2.35 ± 0. 24	2.67 ± 0.33	p=0.077
Postoperative 12th hour	3.46 ± 0.41	4.52 ± 0.62	p=0.024*
Postoperative 24th hour	0.5 ± 0.06	0.7 ± 0.09	p=0.066

* p<0.05 Visuel Analog Scale in Group S was higher than Group C at postoperative 12th hour

VAS score at postoperative 12 hours was significantly higher in subjects receiving spinal anesthesia (4.52±0.62) compared to those receiving caudal epidural anesthesia (3.46±0.41) (p=0.024) (Table 4). Time to first analgesic administration was significantly lower in subjects randomized to spinal anesthesia compared to those receiving caudal epidural anesthesia (p=0.007). There were no significant differences between the groups with respect to the surgeons' or patients' satisfaction.

Discussion

This study showed that caudal epidural anesthesia would provide equal analgesia and les motor block compared to spinal anesthesia in subjects undergoing day-case perianal surgery. The findings in this study indicate that both caudal epidural anesthesia and spinal anesthesia provide similar hemodynamic profile in this patient population. Results of this study also reveal that spinal anesthesia provides more extensive motor and sensorial block compared to those receiving epidural anesthesia. However, postoperative pain is more prominent in subjects randomized to spinal anesthesia; thus, time to first analgesic requirement is shorter in this group of patients. However, both anesthetic techniques are associated with similar surgeon and patients' satisfaction.

Perianal surgical procedures are reported to account for up to 10% of general surgical procedures [21]. Perianal surgery is commonly performed on a day-case basis to reduce health-care costs and shorten unnecessary hospital stay. Consequently, central blocks are frequently utilized in the anesthetic management of subjects undergoing perianal surgery [22]. Regional anesthesia prevents spontaneous breathing and preventative reflexes remain active during the surgery; thus, recovery is rapid and patients can be mobilized in early postoperative period.

Spinal anesthesia with 0.5% isobaric bupivacaine or 2% lidocaine has long been used in anesthetic management of patients undergoing ambulatory anorectal surgery [23,24]. A single dose of isobaric bupivacaine has been reported to result in a block from L5 up to T2 level, which is actually

unpredictable [25]. Hyperbaric spinal anesthesia can provide a more predictable block compared to isobaric spinal anesthesia [23,26]. However, hypotension and bradycardia, which may result in acute cardiovascular disorders, may occur in up to one-third of patients receiving spinal anesthesia [27]. Postdural puncture headache and transitory radicular irritation may also be encountered during spinal anesthesia, particularly with short-acting local anesthetic agents [28,29]. Hemodynamic side effects of spinal anesthesia has been overcome with the use of levobupivacaine, which has a wide margin between the therapeutic and toxic dose, lower cardiac toxicity compared to bupivacaine [30]. Therefore, levobupivacaine was preferred as a local anesthetic in our study. So, adequate anesthesia of the surgical area was provided with the use of levobupivacaine, and no hemodynamically significant side effects were observed in our study.

Caudal anesthesia is a simple and low-cost technique which has been safely used in perianal procedures [31]. Compared to spinal anesthesia, the level of motor block is more predictable with caudal epidural anesthesia [32]. Selective sensorial and motor block provided by caudal epidural anesthesia in the anorectal area without motor block in legs may facilitate early ambulation and discharge [33,34]. Temporary neurologic symptoms and postdural puncture headache, which seldom complicate spinal anesthesia, are rare with caudal epidural anesthesia [35-37]. Moreover, the incidence of hypotension and bradycardia is much lower with caudal epidural anesthesia compared to spinal anesthesia. However, several anatomical variations including upward and downward displacement of the hiatus, pronounced narrowing or partial obliteration of the sacral canal, and ossification of the sacrococcygeal membrane may complicate needle insertion and lead to a failure in performing caudal epidural anesthesia [25]. Nevertheless, the rate of failure is extremely low when the procedure is performed by experienced anesthetists [38]. In this study, caudal blocks were performed by experienced people using traditional methods. Adequate anesthesia level was achieved with this block. No clinically significant complications were encountered.

Both spinal anesthesia and caudal epidural anesthesia are commonly used for the anesthetic management of patients undergoing perianal surgery. However, there is limited research comparing the two techniques in terms of the adequacy of the sensory and motor block, hemodynamic changes, postoperative pain and surgeons' and patients' satisfaction. We hypothesized that caudal epidural anesthesia would provide less motor and sensory block and better intraoperative hemodynamics compared to spinal anesthesia. Our findings show that spinal anesthesia is associated with more extensive motor and sensory block compared to caudal epidural anesthesia. Moreover, no significant differences occurred in MAP and heart rate between spinal and caudal anesthesia. This may particularly explained by the use of levobupivacaine for spinal anesthesia, which has reduced cardiovascular toxicity compared to tradition local anesthetic agents such as bupivacain. We also found out that, VAS score indicating postperative pain at 12th hour was significantly higher in subjects receiving spinal anesthesia compared to those receiving caudal block. Although the sensorial block provided by spinal anesthesia is more extensive compared to caudal block, it appears that durability of the sensory block is shorter with spinal aneshteisa than caudal block. However, the difference in surgical pain at postoperative 12th hour did not translate into patients' satisfaction. This may be associated with the limited number of patients enrolled in the study. Further studies with larger sample size are required to clearly address the effect of caudal block on patients' satisfaction in perianal surgery.

Given that caudal epidural anesthesia provides less extensive motor block compared to spinal anesthesia, patients undergoing day-case perianal surgery with caudal block may be ambulated early in the postoperative period and discharged without delay.

There are some limitations concerning the present study. The sample size is relatively small. Data concerning the time to ambulation and time to urination are lacking. Strict criteria were not used for the discharge of patients in our hospital. Therefore, we cannot clearly state that caudal block has advantages over spinal anesthesia regarding early ambulation and urinary retention. However, limited motor block to anorectal area in our study population makes us speculate that caudal block may facilitate ambulation in subjects undergoing perianal surgery.

Conclusion

Spinal anesthesia is associated with more extensive sensory and motor block compared to caudal epidural anesthesia in patients undergoing perianal surgery. Both techniques lead to similar hemodynamic changes. Postoperative pain control is more favorable with caudal block than the spinal anesthesia. However, neither surgeons nor the patients' satisfaction is different between the two techniques. Lack of motor block with caudal epidural anesthesia may facilitate ambulation and discharger in patients undergoing day-case perianal surgery.

Highlights of the Study

- Advances in anesthetic and surgical techniques led to an increase in outpatient surgical procedures.
- Performing several surgeries in outpatient setting not only reduces healthcare costs but also increases patients' satisfaction due to same day discharge after the procedure
- General anesthesia, local anesthesia, and regional anesthesia techniques have traditionally been used in anesthesia management of patients undergoing perianal surgery

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Mechanical ventilation management in patients diagnosed with Covid-19 who underwent pediatric open-heart surgery

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Abstract

Aim: The new pneumonia pathogen "Covid-19" has been causing the pandemic since December 2019. There has been an increase in the number of cases reported in the pediatric population, particularly in adult patients. In the pediatric population, where asymptomatic transmission is standard, some mandatory protocol changes in preoperative and postoperative mechanical ventilation management must be made concerning pediatric cardiac surgery.

Material and methods: Our study retrospectively reviewed 215 patients operated on in our pediatric cardiac surgery clinic from March 11, 2020, to April 15, 2021. Eleven patients who were asymptomatic preoperatively and had rt-PCR (-) but had rt-PCR (+) in the postoperative period and 15 patients who required emergency surgery and had rt-PCR (+) in the preoperative period were included in the study.

Results: The intensive care period of the patients ranged from 2 to 51 days, with an average of 10.61±13.58 days. The duration of stay connected to the ventilator is 1 to 44 days. It was found that the total time spent on a ventilator was 8.11±13.27 days. The average service follow-up time was 9.23±5.54 days, with a range of 0 to 21 days. Three of the patients required ECMO, and all of those who required ECMO died.

Conclusion: Mechanical ventilation management in pediatric patients should be adjusted according to the patient's unique underlying pathophysiology and conducted under the physician's close clinical supervision. While a lung-protective approach is critical in this patient group, where barotrauma occurs frequently, each clinic should handle the process according to its resources and experience.

Key words : mechanical ventilation, COVID-19, barotruma, pediatric cardiac surgery

Introduction

In December 2019, a new coronavirus strain was added to pneumonia pathogen viruses [1]. Pediatric pneumonia cases have been identified in the later period due to new knowledge about the virus and mutations. However, the outbreak is thought to be mild and asymptomatic in the pediatric population in the early period [2].

Clinicians had to follow some mandatory protocol changes before and after pediatric cardiac surgery operations in the pediatric population where the asymptomatic transition is common during the pandemic [3]. While knowledge on management and treatment methods is still limited, it is not appropriate to tackle the epidemic using a single method. Each country should develop a strategy to tackle the outbreak based on its own experiences, health dynamics, capacity, vaccination rates, and medication availability in the follow-up and treatment of COVID-19 patients [4].

Intensive care beds and mechanical ventilators have become strategically important due to the course of the epidemic. Patients' respiratory support, postural changes, mobilization, and weaning from invasive

mechanical ventilator (MV) support are areas in which respiratory physiotherapists play an important role [5,6]. It is also known that it improves oxygenation in the prone position in adults [7]. In adult Covid-19 patients who need a ventilator due to pulmonary complications, mortality rates range from 24% to 28% [8,9]. Patients with MV can develop pulmonary complications such as barotrauma due to Covid-19 pneumonia [10]. Special ventilation management is required in this patient group, such as a high positive end-expiratory pressure (PEEP) strategy and a low tidal volume [11].

While this whole process continues, babies with congenital heart disease with Covid-19 positivity are born, and these patients need to be operated on urgently. Covid-19 positivity can be detected after preoperative asymptomatic elective cases with Polymerase Chain Reaction (PCR) control along with normalization processes [12]. After open-heart surgery, we plan to present postoperative mechanical ventilation strategies and experiences in patients with Covid-19 PCR positive.

Material and methods

In our study, 215 patients operated in our pediatric cardiac surgery clinic from March 11, 2020, to April 15, 2021, were retrospectively reviewed. 11 patients (42.3%) who were asymptomatic and PCR (-) preoperatively but had PCR (+) postoperatively, and 15 (57.6%) patients with PCR (+) in the preoperative period who required emergency surgery and underwent surgery were included in the study.

Our study is a retrospective, observational, single-center case series study. The patients' age, gender, weight, diagnosis, previous operations, treatment, mechanical ventilation, and PCR results were recorded. All patients with Covid-19 positivity were followed up in the isolation units of our clinic's intensive care unit.

Regardless of the Covid-19 PCR positive or negative difference, all patients were intubated with a video-assisted laryngoscope in the preoperative phase. During the operation, a virus filter was used. It was only used during surgery if aspiration was necessary. Furthermore, closed aspiration systems were used.

To of the risk of infection with repeated procedures in patients with proven Covid-19 positivity, the team was reduced to the minimum, and the most experienced people intubated patients. Until intubation, neuromuscular blockers were used to suppress cough in patients without a history of the difficult airway. The dead spaces of the viral filters were calculated, and our tidal volume was modified accordingly. Respiration rates were adjusted based on the children's ages and blood carbon dioxide levels.

The cuff part of the intubation tube was inflated and followed to avoid aerosol contamination in intubated patients. Cuff pressure (20-30 mmHg) was monitored daily. A nasogastric tube was placed after tracheal intubation was completed and ventilation was provided safely.

In addition to surgical antibiotic prophylaxis, vitamin C, and vitamin D aspirin to support the immune system, all patients were started on LMWH for pulmonary embolism prophylaxis in the postoperative period. Nebules were routinely applied to the patients during mechanical ventilation with the aid of an antiviral filter via a nebulizer.

In all of the patients, the same type of ventilator was used (Maquet SERVO-i intensive care ventilator). Except for patients with particular pathologies (patients with single ventricle physiology) and heart failure, where intrathoracic pressure affects venous and pulmonary return, PEEP (Positive End-Expiratory Pressure) was used to decrease alveolar collapse, thus avoid atelectasis in all patients.

Patients were ventilated with pressure control. It aimed to protect the lungs from barotrauma by maintaining the tidal volume at a minimum level according to the patient's need, with a goal of 4-8 mL/Kg. In patients in need, the tidal volume was increased according to the patient's needs.

The patients were MV under sufficient neuromuscular blockade (rocuronium 10-12 mcg/kg/min), sedation (midazolam 0.05-0.6 mg/kg/h), and analgesia (fentanyl 1) infusions before extubation was considered to prevent pulmonary damage caused by transpulmonary pressure fluctuations caused by the patient's own effort. After extubation, sedation (dexmedetomidine 0.2-2.0 mcg/kg/hour) infusion was used.

Attention was paid to immune modulation, and steroid therapy was initiated in patients with severe disease to protect the lungs from cytokine release from biotrauma.

Fio2 values were held as low as possible in all patients to protect against the adverse effects of oxygen radicals produced due to high oxygen.

Only when clinically necessary was aspiration performed, with the parameters of saturation and blood gases being monitored.

Patients were regularly placed in the intermittent prone position as long as they were on mechanical ventilation.

The patients were extubated in the intensive care unit after adequate spontaneous breathing and airway reflexes were detected. Response to simple instructions, oropharyngeal temperature greater than 36.5°C, hemodynamic stability, and the absence of uncontrollable arrhythmias were considered when deciding whether or not to extubate. In addition, in arterial blood gas analysis, the condition was sought that the pH should be more than 7.30, the FiO2 should be less than 50%, the PaO2 should be higher than 60 mmHg, and the PaCO2 should be higher should be lower than 45 mmHg. Early mobilization, postural drainage, and breathing exercises were conducted in the presence of our expert respiratory physiotherapists during the MV separation of the patients during the postoperative period.

All personnel working on the Covid-19 patient follow-up were provided with protective masks and visor equipment. Isolation of the follow-up personnel from other patients and personnel were given to prevent contamination of other patients.

High flow nasal oxygen support was performed with a mask to prevent aerosol exposure in potential patients, and HFNO support was avoided in cases of patient incompatibility.

Sildenafil (0.5-2 mg/kg/dose every 4-6 hours, maximum 20 mg/dose every 8 hours) and nitric oxide were started in patients who did not respond to treatment. Venovenous and venoarterial ECMO were used in patients who did not respond.

Permission was obtained from the Ministry of Health for the study. It was made retrospectively in compliance with the Declaration of Helsinki by observing ethical rules.

For statistical analysis, the NCSS (Number Cruncher Statistical Systems) 2007 software (Kaysville, Utah, USA) was used. Descriptive statistical methods (Average, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum) were used to evaluate the study data.

Results

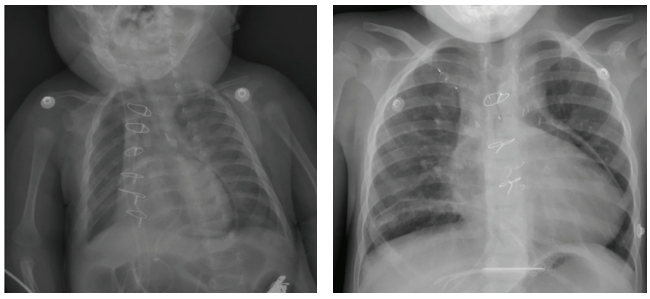
In our postoperative intensive care unit, 26 patients were followed up. 15 of them were female (57.6%), 11 were male (42.3%). 4 out of 26 patients died (mortality 15.38%). 5 patients received prolonged ventilation (>14 days), pneumopericardium in 2 patients, pneumothorax in 3 patients, and prolonged antibiotic

therapy for pneumonia in 5 patients. Out of the 26 patients, CPB was used in 19 of them. Subcutaneous emphysema was seen in 1 patient. Pulmonary embolism was not observed in any patient. Due to a gastric tolerance disorder, four patients were initiated on parenteral nutrition. 3 patients needed ECMO, and all of the patients requiring ECMO died.

Patent Ductus Arteriosus closure (n=2), Ebstein Cone repair (n=1), Atrial septal defect closure (ASD) (n=1), Ventricular septal defect (VSD) closure (n=2), ASD and VSD closure (n=1), Tetralogy of Fallot total correction (n=3), total anomalous pulmonary venous return repair (n=1), pulmonary banding (n=1), modified Blalock-Taussig shunt (n=1), VSD and PDA Closure (n=1), Aortic ridge resection (n = 1), arterial switch operation (jatenne procedure) (n=2), Aortic arcus reconstruction (n=3), End to end aortic coarctation repair (n=2), Drain insertion due to pericardial effusion (n=1), The Norwood stage1 (n=2) in hypoplastic left heart syndrome, Fontan procedure (n=1) were performed.

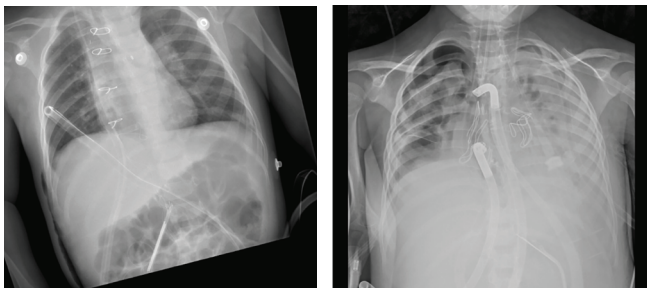
A 4-year-old female patient who underwent the Fontan procedure, two patients who underwent the Norwood stage 1 procedure, and a 12-day female patient who underwent the arterial switch procedure are patients with Ex.

Figure 1 - Image of 2 different patients with pneumopericardium



In two patients who underwent Arcus reconstruction and VSD closure, postoperative pneumopericardium developed and disappeared in their follow-up.

Figure 2 - ECMO patient with subcutaneous emphysema and Right pneumothorax



Subcutaneous emphysema regressed in patients with subcutaneous emphysema who were followed up on and needed no additional treatment. The patient, who had Fontan surgery, needed ECMO in the postoperative period, as his lung parenchyma rapidly deteriorated and his pneumothorax persisted amid thoracic drains. The patient died on the 28th day after surgery.

The 26 patients included in the study ranged in age from 13 days to 187 months, and the average was found as 30.21±51.45 months. The patients' weights ranged from 2.2 to 42 kilograms, and the mean was detected as 10.68±11.15 kilograms. The patients' cardiopulmonary bypass duration ranged from 0 to 1182 minutes, and the average was found as 84.88±61.07 minutes. The cross-clamp period is between 0 and 154 minutes, and the mean was determined as 66.96±52.93 minutes.

Figure 3 - Ventilator view of a patient needing prolonged ventilation under full sedation (a) and a patient considering extubation (b)

Table 1 Demographic, Postoperative parameters

	N	Minimum	Maximum	Mean	Std. Deviation
AGE		0.13	187.00	30.21	51.45
WEIGHT		2.20	42.00	10.68	11.15
CPB (min)		0.00	182.00	84.88	61.07
CC (min)		0.00	154.00	66.96	52.93
ICU		2.00	51.00	10.61	13.58
VENTILATION (day)		1.00	44.00	8.11	13.27
SERVICE (day)		0.00	21.00	9.23	5.54
Valid N (listwise)	26				

The intensive care period of the patients ranged from 2 to 51 days, with an average of 10.61±13.58 days. The duration of stay connected to the ventilator is 1 to 44 days. It was determined that the total time spent on a ventilator was 8.11±13.27 days. The service follow-up duration ranged from 0 to 21 days, and the average was found to be 9.23±5.54.

Table 2 Postoperative Ventilator Parameters of the Patients

	N	Minimum	Maximum	Mean	Std. Deviation
Fio2		21.00	100.00	50.5000	20.31403
frequency		20.00	42.00	31.7308	4.96030
Ppeak		13.00	38.00	19.6154	6.30604
PEEP		.00	11.00	5.0385	2.59970
Tidal (total)		12.00	336.00	88.4358	94.99249
Tidal (kg/ml)		4.20	14.80	7.3323	2.22477
weight		2.20	42.00	10.6846	11.15404
Valid N (listwise)	26				

The patients' postoperative FiO2 values ranged from 21% to 100%, with an average of 50.50±20.31%. The patients' postoperative minute respiratory rate (respiratory frequency) ranged between 20 and 42; its average was determined as 31.73±4.96. The peak pressures of the patients in the postoperative ventilator were found between 13 and 38 Ppeak; its average was calculated as 19.61±6.30. Patients' positive exhalation pressures (PEEP) ranged from 0 to 11, with a mean of 5.03±2.59. The tidal volumes of the patients ranged from 12 mL to 336 mL and were calculated as 88.43±94.99 on average. Tidal volumes per kilo of patients ranged from 4.2 kg/mL to 14.8 kg/mL and were measured as 7.33±2.22.

Discussion

Intensive care beds and mechanical ventilators have become more critical due to the COVID-19 pandemic's increasing need. We want to share our knowledge and experience managing mechanical ventilation after open-heart surgery in COVID-19 positive pediatric patients, a complex, challenging, and experience-demanding population for mechanical ventilation.

Endotracheal intubation is known to have the most significant risk since the person performing the procedure would perform the process with their face very close to the patient's airways. It is necessary to use personal protective equipment, an intubation tube of suitable size, and to be done by experienced people [8]. Preoperative intubations are performed in our clinical practice under deep anesthesia using a cuffed intubation tube, with adequate personal protective equipment, and by the team's most experienced members.

Intubation under deep anesthesia is considered to minimize infection because it suppresses reflexes, including coughing and sneezing, which carry a high risk of viral transmission [9]. Patients were intubated with adequate neuromuscular blockade, sedation, and analgesia in our clinical practice and monitored with MV.

In the treatment of COVID-19 patients, postoperative changes, mobilization, and respiratory physiotherapy conducted by specialist physiotherapists, as highlighted in the study by Lazzeri et al., play an essential role in the correction of hypoxia and patient separation from the mechanical ventilator [10]. In the postoperative period, we also provide respiratory physiotherapy, mobilization, and postural drainage by our specialist physiotherapist to all of our patients, whether they are COVID-19 positive or not.

In their study of patients who needed mechanical ventilation due to Covid-19 pneumonia, Udi et al. reported 40% barotrauma despite lung-protective MV strategies [11]. We found pneumopericardium in two patients, pneumothorax in three patients, and subcutaneous emphysema in one patient in our postoperative case series. We believe that lung damage (alveolar rupture) secondary to pulmonary fibrosis and adhesions caused by the Covid-19 virus triggers barotrauma. Based on our own experience with these patients who are more prone to pulmonary problems, we used our lung-protective mechanical ventilation strategy. Despite this, we encountered more barotrauma in this group compared to the normal population.

Mechanical ventilation strategies should be designed following the specific underlying pathophysiology, and the strategy should be reviewed regularly. Lung expansion should be adjusted appropriately, the patient should be protected from atelectasis, and high tidal volume should be avoided [12]. By blinding them to the patients' blood gas parameters, we adjusted the tidal volume of the patients at 4-8 mL/kg 4 times a day (1 in 6 hours) in our clinical practice. We tried to keep the patients' tidal volume to a minimum based on their needs.

In their study of the Covid-19 positive pediatric population, Sankar et al. presented their treatment and follow-up strategies to the literature [13]. We have also developed our follow-up and treatment plan for patients who test positive for Covid-19. In addition, we used a cuffed tube in all patients and tried to prevent the spread of the virus to healthcare personnel by strict isolation measures.

Although viral filters decrease transmission from patients to healthcare professionals, they add 10-40 mL of dead space to the system [14]. We calculated these dead spaces in our clinical practice and modified our tidal volume accordingly. The respiration rates were adjusted based on the children's ages and blood gas carbon dioxide levels.

In a study conducted in Brazil, Prata-barbarasa et al. stated that the prognosis was strong in children under one year; patients with high inflammatory biomarkers had a bad prognosis [15]. Aminophylline (infusion therapy 0.4 mg/kg/hour dose) and budesonide (inhaled corticosteroid 500 g/dose) were given to protect patients requiring prolonged intubation and ECMO from inflammatory biotrauma and bronchodilation. Despite this, five patients needed prolonged ventilation.

There are opinions that high-flow oxygen therapy may increase droplet transmission in viral infections. If high-flow oxygen therapy is to be used, a mask should be placed on the patient after the nasal cannulae have been placed. In addition to the N95, FFP2, and similar masks, healthcare workers who regularly care for patients requiring oxygen therapy or non-invasive mechanical ventilation (NIMV) should use personal protective equipment (gloves, gowns, safety glasses, or face shields). If NIMV is to be applied to the patient, it should be applied in a negative pressure room, if possible [16,17]. We avoided High-flow oxygen therapy as much as possible in our clinical practice and only used it in one patient.

Burton-Papp et al. reported in an adult study that the prone position can improve oxygenation in Covid-19 patients [18]. In our pediatric patient group, we still use the prone position frequently, and we think it positively impacts the patients' pulmonary condition.

In patients with excessive volume loading MV or left ventricular failure, cardiac "output" may increase due to decreased venous return, reducing left ventricular afterload, and increasing circumferential positive intrapleural pressure. Patients who are provided positive end-expiratory pressure may experience hemodynamic side effects (PEEP). During positive pressure ventilation, a decrease in cardiac "output" and a slight decline in systemic blood pressure is observed. Reduced perfusion can exacerbate the ventilation/perfusion mismatch and decrease oxygen delivery to tissues. As a result, organ damage increases, and complications may occur [19]. We adjusted the PEEP values for our patients when applying PEEP to prevent atelectasis in MV, taking into account their pathophysiology. We believe that the PEEP values of these patients in the postoperative period are much more important for patient prognosis than predicted.

Dhont et al. stated in their research that lung expansion and mechanics were well maintained in the early days of the disease. There was no rise in airway resistance or dead space, so the patient would not experience respiratory discomfort. There could be a false sense of well-being. However, they did note that sudden and rapid respiratory decompensation can occur in this patient group, with tachypnea and hyperpnea being the most significant clinical warning signs of respiratory failure in COVID-19 patients [20]. We aimed to diagnose potential clinical deterioration in postoperative intensive care by conducting near blood gas monitoring and routine chest X-ray and biochemistry tests at 6-hour intervals four times a day.

While pediatric intensive care medicine has advanced rapidly over the last decade, much data on mechanical ventilation guidelines in children have been omitted from adult studies. The need for well-designed pediatric randomized controlled experimental and clinical trials to optimize pediatric ventilator interaction is demonstrated [21]. Even before the pandemic, the COVID-19 positivity of pediatric patients following open-heart surgery, for whom mechanical ventilation control takes significant clinical experience and effort, compelled us to

establish a strategy that protects both the patient and healthcare professionals. We developed our clinical protocol based on published adult and pediatric Covid-19 -19 studies and our prior clinical experience.

According to Marraro et al., effective therapies to prevent progressive lung damage are essential for the prognosis of patients who test positive for Covid-19. They can help reduce complications in intensive care [21,22]. Additionally, we started all patients on LMWH in the postoperative phase for vitamin C and D supplementation and pulmonary embolism prophylaxis.

Conclusion

In postoperative Covid-19 rt-PCR positive pediatric patients, the information found in any mechanical ventilation protocol cannot substitute for a physician's professional judgment, cannot be used alone for diagnosis or treatment, and can only direct the physician in light of general information. Pediatric mechanical ventilation should be adjusted according to the patient's unique underlying pathophysiology and should be done under the physician's close clinical supervision. While lung protection is essential in this patient group because barotrauma occurs frequently, each clinic should manage this process according to its resources and experience.

Limitation: Our study is a single-center retrospective study, and studies with large populations are needed to establish precise protocols.

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The functional post-op rehabilitation results in the trimalleolar ankle fracture: A one-year follow-up of the case

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Abstract

The aim of this study was to evaluate the one-year results of the effects of an eight-week functional rehabilitation program on pain, swelling, range of motion, balance, fear of movement, functional status of the ankle, and quality of life in a patient with a surgically treated trimalleolar ankle fracture. In the study, pain (Visual Analogue Scale), ankle joint swelling (Figure of eight methods), range of motion (Universal goniometer), static balance performance (Flamingo Balance Test), fear of movement (Tampa Kinesophobia Scale), functional status of the ankle (Foot Function Index) and quality of life (SF-36 Health Survey) were assessed. An eight-week functional rehabilitation program was applied to the patient after 8th week from surgery. Assessments were repeated before and after functional rehabilitation program, and at the one-year follow-up. At the end of the functional rehabilitation program and in one-year follow-up, it was found that pain, swelling, and fear of movement decreased, range of motion, balance, functional status of the ankle, and quality of life increased. In trimalleolar ankle fractures, a well-planned functional physiotherapy and rehabilitation program after surgery can support surgical treatment by reducing the patient's symptoms and fear of movement, increasing functional capacity and quality of life.

Key words: ankle fracture, post-op treatment, physiotherapy, rehabilitation, one-year follow up

Introduction

Ankle fractures are among the most common fractures in the lower extremity [1]. These fractures are classified as unimalleolar, bimalleolar, or trimalleolar based on the number of malleolus involved in the fracture. Unimalleolar fracture refers to the fracture of either medial or lateral malleolus, while bimalleolar fracture describes fractures of both malleoli. The majority of ankle fractures comprise these fractures. A trimalleolar ankle fracture (TAF) is a type of complex ankle fracture that includes a posterior malleolar fracture in addition to the bimalleolar fracture. It is the rarest type that presents in 7% of all ankle fractures and generally occurs with high-energy trauma [1,2].

While most of the ankle fractures are stable isolated malleolus fractures, some are unstable fractures. Unstable ankle fractures where malleoli are displaced are treated with surgical fixation with screws or plates [2]. In order to prevent instability and degenerative changes in posterior malleolus fractures that involve more than 25% of the articular surface (tibial plafond), fixation of the posterior fragment is provided by indirect method with lag screw or posterior direct approach [3]. After surgical treatment, patients often experience pain, swelling, stiffness, and loss of mobility [4]. It is crucial to apply an effective physiotherapy and rehabilitation program to prevent these problems and increase the functional status of the patient after surgery [2]. Reflex sympathetic dystrophy is a complex disorder affecting neural, vascular, bony, and soft tissue structures that can be seen in some patients with ankle fractures. It is characterized by pain, trophic changes (in structure in both deep and superficial tissues), sensory abnormalities, sweating and

abnormal blood flow, stiffness, and functional impairment. A proper rehabilitation program can help reduce hypersensitivity and prevent contractures by providing cartilage nutrition and periarticular circulation in the joints [5].

The goals of the functional rehabilitation program (FRP) in ankle fracture are to treat the symptoms, restore or maintain range of motion (ROM), strength, proprioception, prevent the deterioration of the balance of strength and provide early functional mobility. Therapeutic modalities and exercise are components of ankle rehabilitation [6]. A very few studies have examined the effects of rehabilitation programs after surgically treated ankle fractures, and the reported results are controversial [1]. Also, there is no specific protocol for surgically treated TAF rehabilitation in the literature. The aim of this study was to evaluate the one-year follow-up results of the effects of an eight-week FRP on pain, swelling, ROM, balance, fear of movement, functional status of the ankle, and quality of life in a patient with a surgically treated TAF.

Case presentation

A 24-year-old female patient experienced an eversion left ankle (non-dominant foot) sprain as a result of a fall from a height. TAF in the ankle was detected by computed tomography (CT) (Figure 1). Surgical treatment was performed with the Open Reduction Internal Fixation method. With a standard incision of approximately 15 cm just above the lateral malleolus, the lateral malleolus and the posterior malleolus (antero-posterior lag screw) were fixed with the three and one cannulated screws, respectively (Figure 2). The patient's ankle was immobilized in a cast for eight weeks. When she applied to our clinic after the 8th week from surgery, had complaints of severe ankle pain during rest and activity, swelling, difficulty in walking, and climbing up and downstairs.

Figure 1 -Left ankle CT

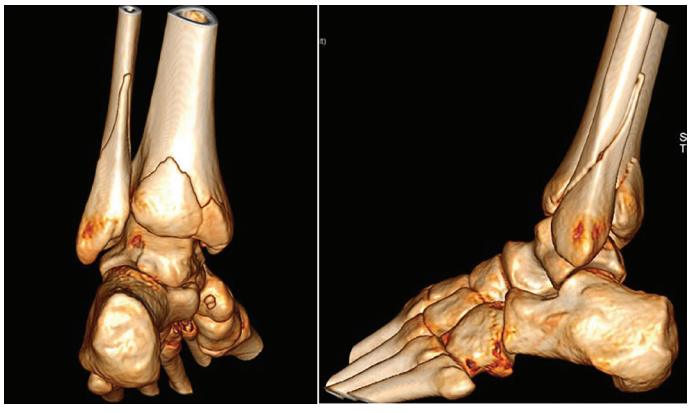
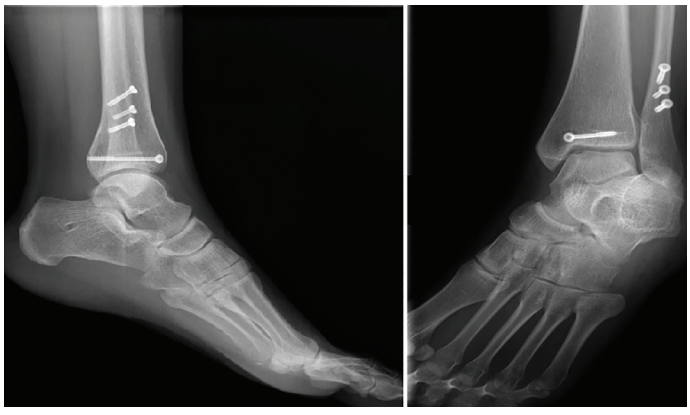


Figure 2 -Left ankle radiography



After obtaining verbal and written consent in the post-op 8th week, the patient was included in the rehabilitation program after baseline assessments. The intensity of the pain at rest, activity and night of the peri ankle area was evaluated with the Visual Analogue Scale (VAS) [7]. The figure of eight shaped measurement method was used to evaluate the ankle joint swelling [8]. Dorsiflexion, plantar flexion, inversion and eversion passive range of motion of the ankle were measured with a universal goniometer. Static balance performance was evaluated for the left and right sides with the Flamingo Balance Test in eyes-open and eyes-closed positions. The score was recorded in seconds that it was able to maintain balance [9]. Fear of movement was assessed using the Tampa Kinesophobia Scale (TKS). TKS is a valid and reliable scale that consists of 17 questions used to assess fear of movement in problems related to the musculoskeletal system. The scale scores between 17 and 68 in total, and higher scores indicate that the fear of movement is high [10]. The Foot Function Index (FFI) was used to assess the functional status of the affected foot. The scale was developed to evaluate the impact of foot and ankle pathology on function in terms of pain, disability and activity restriction. The FFI is a self-administered scale consisting of 23 items divided into three subscales [11]. Quality of life was evaluated with the SF-36 Health Survey. SF-36 consists of two subsections as Physical Component Score (PCS) and Mental Component Score (MCS) and a total of 36 questions. High scores indicate a high quality of life [12]. Turkish validity and reliability of all scales used in this study were confirmed [10-12]. All assessments were repeated before and after the eight-week FRP and at one-year follow-up.

A total of 24 sessions of FRP, including eight weeks, three sessions a week, was applied to the patient. According to the patient's tolerance, the rehabilitation program was progressed through increasing activity speed and duration, varying the stability of the surface on which the patient, from double-leg to single-leg stance and from eyes-open to eyes-closed without any symptoms. In the first two weeks, the Transcutaneous Electrical Nerve Stimulation and vacuum interferential therapy was applied for 20 and 15 minutes respectively to decrease pain and swelling. Ankle mobilization and friction massage was performed to remove the adhesions and increase mobility in the ankle. Since the proximal tibiofibular joint is closely related to the ankle joint and can affect ankle mobility, mobilization for the proximal tibiofibular joint was added to the treatment program to increase the mobility of the ankle and proximal tibiofibular joint. Stretching exercises with the knee extended and flexed were included in the program to increase the Achilles tendon flexibility. As soon as a painless ROM was achieved, eccentric and concentric resistance strengthening exercises with Thera-band® elastic band were initiated and continued (Figure 3/A). In order to increase the balance and proprioception in the patient who felt poor balance confidence while weight-bearing to the left side, weight-bearing and squat exercises on stable and then unstable floors was added in the advanced stages of the rehabilitation program. The progress in these exercises was made from double-leg to single-leg stance and from eyes-open to eyes-closed (Figure 3/B).

It was found that there was a decrease in pain and ankle joint swelling, an increase in ROM and balance in the left ankle after treatment and at one-year follow-up (Table 1).

After treatment and at one-year follow-up, there was a decrease in the FFI sub-scale scores and the TKS score, and an increase in the scores of the PCS and MCS subsections of the SF-36 scale (Table 2).

Figure 3 A -Resistance strengthening exercises with Thera-band®, **B**: Balance and proprioceptive training on uneven surfaces

Table 1 Changes in pain, ankle joint swelling, ROM, and balance parameters in the left ankle

		Right	Effected Foot		
			BT	AT	1-YF
VAS	Pain at rest	0	6.3	0	0
	Pain during activity	0	8.5	2.3	0
	Pain at night	0	8.2	0	0
Ankle joint swelling (cm)		53	57.8	54.3	53.4
ROM (°)	Dorsiflexion	16	5	13	15
	Plantar flexion	44	14	39	42
	Eversion	18	3	14	16
	Inversion	48	11	44	46
Balance (second)	Eyes-open	94.8	10.7	88.2	92.3
	Eyes-closed	55.6	5.5	49.4	52.7

AT: After treatment, BT: Before treatment, ROM: Range of motion, VAS: Visual analog scale, 1-YF: One-year follow-up

Table 2 Improvement levels in FFI, TKS and SF-36 scale scores

			BT	AT	1-YF
FFI	Pain (%)		58.7	17.5	0
	Disability (%)		67.9	14.8	3.7
	Activity restriction (%)		80	4.4	0
TKS			60	21	17
SF-36 Health Survey		PCS	24.5	93.7	100
SF-36 Health Survey		MCS	31.25	90	100

AT: After treatment, BT: Before treatment, FFI: Foot Function Index, MCS: Mental Component Score, PCS: Physical Component Score, TKS: Tampa Kinesophobia Scale, 1-YF: One-year follow-up

Discussion

Foot and ankle pathologies lead to restriction of daily living activities, balance and walking problems. As a result of these problems, the functional status and quality of life of the person decrease [11]. Ankle fractures are the most common type of lower extremity fracture. TAF is the rarest type of ankle fracture. In TAF, it is considered essential to provide anatomic reduction with the appropriate surgical methods and to apply for an effective rehabilitation program after surgery in order to prevent instability and osteoarthritis in the future [2,3]. In the present study, an eight-week FRP was applied to the patient in which a TAF was surgically treated. It was observed that the pain and swelling in the ankle of the patient were decreased after the FRP, and completely disappeared in a one-year follow-up. It was found that ROM and balance increased after FRP, and these parameters reached approximately the same values as the right side at one-year follow-up. In addition, it was found that fear of movement decreased, functional status of the foot and quality of life increased.

Nilsson et al. [1] compared the 12-weeks individual training program with the usual care in patients with surgically treated ankle fractures. In this study, in which symptoms, functional status, ankle mobility, quality of life, and walking performance were evaluated, it was reported that the individual training program was superior to the usual care in patients under the age of 40. In addition, it was reported that more studies are needed to investigate the effectiveness of rehabilitation programs in patients with ankle fractures surgically treated [1]. Hong et al. [4] have been evaluated 31 patients with operatively managed TAF at 1 year postoperatively and found that 52.4% of patients had residual pain, 61.9% of patients had persistent ankle stiffness, 47.6% of patients had swelling. Also, they reported that 66.7% of patients were not able to return to sports, and 25% of patients were unable to do sports at all. In our study, at the one-year follow-up, it was seen that the patient had no residual pain and swelling. Also, the ROM of the left ankle increased and reached similar values with the right side. In the present study, the improvements we achieved in the symptoms, functional status, and quality of life of the patient indicate the importance of FRP in surgically treated TAF.

In the literature, it is reported that balance and proprioception training included in the rehabilitation program after ankle injury may have beneficial effects on postural stability, coordination, and proprioception [13]. For our case report, consistent with the literature, it was found that the patient's balance in eyes-open and eyes-closed positions increased after the FRP, and this improvement was preserved in a one-year follow-up. It has been reported that in patients with fractures, various complications, especially pain, caused by the fracture can cause fear of movement [14]. In the present report, considering the TKS score, it was found that the patient's fear of movement significantly decreased after the FRP and at the one-year follow-up. Following the surgically treated TAF, considering patients' fear of movement, and encouraging them to move, and weight-bearing the affected side can positively affect the rehabilitation process.

In the present study, we found that after the eight-week FRP, the foot function improved according to FFI subscales, and this improvement was preserved in a one-year follow-up. Our reason to use the SF-36 to evaluate the quality of life in our study was that it has been widely used in orthopedics and had strong evidence of validity in evaluating the results of ankle fractures [15,16]. In our study, it was thought that the decrease in pain and fear of movement and the improvement of ROM, balance parameters, and foot function after FRP were effective in increasing the quality of life. The improvements in SF-36 scores in our study are consistent with previous reports [15,16].

It can be considered as a limitation of this study that no measurement was made for proprioception assessment.

In trimalleolar ankle fracture, a well-planned functional physiotherapy and rehabilitation program after surgery can increase the success of surgical treatment by reducing the patient's symptoms and fear of movement, increasing functional capacity and quality of life.

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