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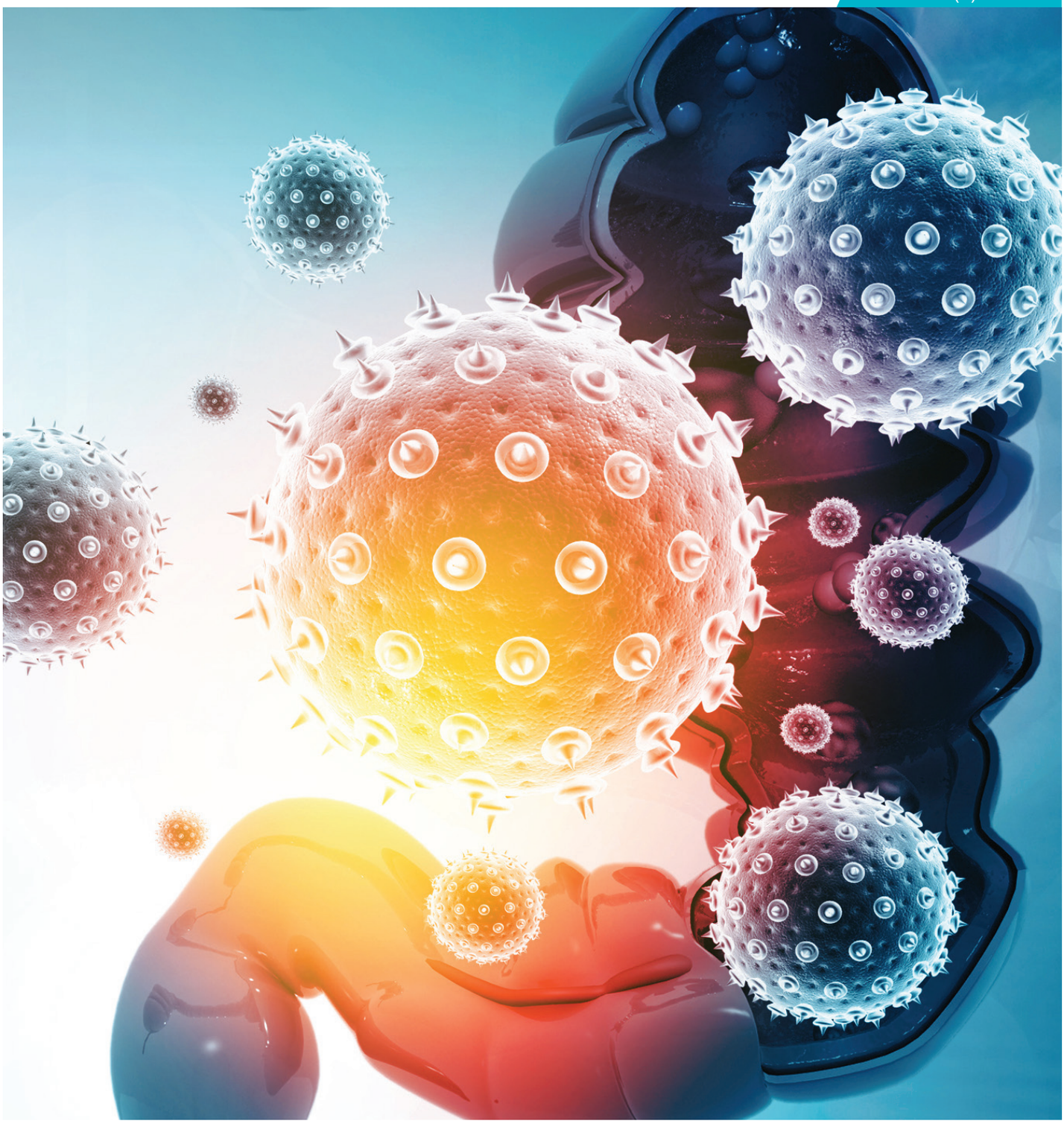

The Incidence of Pharyngeal Cancer in the Republic of Azerbaijan for 2019–2022

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EDITORIAL

AIMS AND SCOPE OF THE JOURNAL

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 Center” publishes the journal bimonthly in a year (in February, April, June, August, October, and December).

All articles sent to editors undergo double-blind review. Manuscripts are judged by two experts exclusively on the basis of their contribution to initial data, ideas and their presentations. Editors accept articles for consideration and publication at no cost. Detailed information is available in the section Information for authors at the end of this material.

The Journal of “Clinical Medicine of Kazakhstan” to the full extent is wedded to initiative of open access and ready to provide free access to full texts of articles, as soon as they will be published and available in the Internet (www.clinmedkaz.org).

Journal was registered in the Ministry of Information of the RK on 05.04.2004 and currently included to the list of Publications, approved by the Committee for Control of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan for publication of the main outcomes of scientific activity.

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The latest HIFU installation- JC therapy has been in use in NSMC since January 2010. This installation allows noncontact complete eliminating the endogenic tumor using high intensity focused ultrasound without cutting the tissues and injury of not affected organs.

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HIFU-therapy of echinococcosis and alveococcosis developed in the clinic is the one and only in the world and is an alternative to surgical treatment of this disease, causing the economic feasibility.

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Acknowledgment to JCMK Editorial Board and Peer-Reviewers for contribution in 2024

Yekaterina Dotsenko

Executive Secretary of the Journal of Clinical Medicine of Kazakhstan

J Clin Med Kaz 2025; 22(1):4-6

Abstract

The publication summarizes the results of the activities for the Journal of Clinical Medicine of Kazakhstan in 2024. It was prepared on behalf of the editorial team of the Journal to express appreciation to all editorial and advisory board members, reviewers and authors who contributed to this journal throuout the year.

On behalf of the editorial team of the Journal of Clinical Medicine of Kazakhstan, we would like to express our appreciation to all editorial and advisory board members, reviewers and authors who contributed to this journal in year 2024.

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OUR STATISTICS

Journal of Clinical Medicine of Kazakhstan published 6 regular issues in 2024:
– Volume 21, Number 1 (2024) with 17 articles;
– Volume 21, Number 2 (2024) with 16 articles;
– Volume 21, Number 3 (2024) with 8 articles;
– Volume 21, Number 4 (2024) with 14 articles;
– Volume 21, Number 5 (2024) with 10 articles;
– Volume 21, Number 6 (2024) with 17 articles.
The acceptance rate of articles in 2024 was 48%: 66 articles received in 2024 were accepted for publication and 72 articles were rejected. The remaining 16 articles published in 2024 were received in 2023 and were taken into account in the statistics for 2023.

AUTHORS 2024

Authors and coauthors who contributed to this journal in 2024 were from the following countries: Azerbaijan, Bulgaria, China, Cyprus, India, Iraq, Japan, Kazakhstan, Libya, Moldova, Nigeria, Pakistan, Spain, Sri Lanka, Sweden, Turkey , Ukraine.

The editorial team of the Journal of Clinical Medicine of Kazakhstan would like to express gratitude for your valuable support and being part of our excellent team. We appreciate your continuous efforts and hope to continue receiving your great feedback, valuable ideas, and interesting scientific papers to further improve the quality and impact of the Journal of Clinical Medicine of Kazakhstan.

In addition, we would like to express heartfelt thanks to all those who contributed to the editorial process and the successful indexing of the journal in Scopus.
Sincerely yours,
Editorial team of the Journal
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Coronary Artery Ectasia and Aneurysm

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Abstract

Coronary artery aneurysms and ectasia are often incidentally diagnosed and may cause arrhythmia, ischemia, rupture, thromboembolism, and heart failure; in adults are caused by atherosclerosis, in pediatrics Kawasaki disease and Takayasu arteritis are main factors. Others are connective tissue disorders, infections, vasculitis, and genetics. Authors comment on recent literature data.

Keywords: aneurysm; coronary artery; ectasia

Dear** Journal of Clinical Medicine of Kazakhstan **Editors,

The long-term outcomes of revascularization in patients with multivessel coronary artery disease and comorbidity have been a major concern, as exposed by the review of Madiyeva MI and colleagues, published in this Journal [1]. The objective of this letter is additional comment on issues of coronary aneurysm (CAA) and ectasia (CAE) [2–10].

CAA may be congenital or acquired, fusiform or saccular, single or multiple, 1.5 times larger than adjacent normal artery segments [2, 9]; CAEs occur in up to 8% of atherosclerotic patients, being found by coronary angiography in up to 5.3% of cases [3, 9]. Atherosclerosis precedes up to 50% of these changes in adults, while Kawasaki disease Takayasu arteritis, and Ehlers-Danlos syndrome are main causes in pediatrics [2, 6]. Additional etiologies include systemic connective tissue diseases, infections, vasculitis, congenital anomalies, genetic factors, and idiopathic [9]. Complications are spasm, thrombosis, embolization, rupture, and compression [9]. Targeted treatments avoid the CAA and improve outcomes [2]. Matrix metalloproteinases, inflammatory cytokines, and growth factors may promote arterial wall remodeling with weakening, favoring the CAAs; growth factors act in angiogenesis and vascular remodeling [2].

A 54-year-old diabetic man with hypertension and dyslipidemia had chest pain and coronary angiography showed right CAE the left anterior descending artery [3]. He became asymptomatic using heparin, aspirin, clopidogrel, angiotensin-converting enzyme inhibitor, beta blocker, statin, and Rivaroxaban, for two years of follow-up. [3]. A 50-year-old hypertense male had severe aortic regurgitation and paroxysmal nocturnal dyspnea; the angiography study showed multiple coronary segments; he was successfully managed by the aortic valve replacement [3]. A 67-year-old diabetic man with dyspnea on exertion had angiography images of the right, circumflex, and left anterior descending coronaries with large diameters; he was treated by aspirin, beta blocker, statin, Dapagliflozin, and Rivaroxaban [3]. A 51-year-old hypertense man had typical angina and the angiography showed CAEs in the left anterior descending and proximal circumflex; he became asymptomatic using aspirin, beta blocker, statin, and Rivaroxaban [3]. A retrospective study compared 260 CAE patients with 419 controls, the average ages: were 59.9 years, and t 38.3% of CAE patients had higher levels of RC than controls; there was association between the levels of RC and elevated risk of CAE [4]. A retrospective evaluation among 16600

patients who had coronary angiography showed isolated CAE in 1.7%; and left anterior descending artery was more affected (52%) [5]. A 79-year-old hypertensive and dyslipidemic man with atrial fibrillation was diagnosed with right CAA, the lesion was at the proximal right coronary, with a maximum diameter of 9 mm and an extension of near 18 mm [6]. A retrospective comparison between primary and secondary outcomes and predictors of mortality of ad-hoc versus planned percutaneous coronary intervention (PCI) in CAE, included 3,179 CAEs (ad-hoc PCIs: 1,286 and planned PCIs: 1,893) [7]. An adolescent with Ehlers-Danlos syndrome had electrocardiographic and biomarker patterns of infarction; CAEs were found in the left coronary and the anterior descending branch, the left circumflex branch, and the right coronary were occluded [8].

Reporting rare entities may reduce the underdiagnosed and misdiagnosed cases.

Authors' Contributions: Conceptualization, V. M. S, A. P. T., J. C. M.; investigation, V. M. S., A. P. T., J. C. M.; verification, V. M. S., A. P. T., J. C. M.; writing – original draft preparation, V. M. S., A. P. T., J. C. M.; writing – review and editing, V. M. S. The authors have read and agreed to the published version of the manuscript.

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Response to the Letter: “Coronary Artery Ectasia and Aneurysm”

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Abstract

Coronary artery aneurysms (CAA) and ectasia (CAE) are significant yet underdiagnosed conditions that influence coronary artery disease (CAD) outcomes. Although CAA and CAE were not included or considered in our study, they undoubtedly have the potential to impact revascularization outcomes.

Keywords: Coronary artery disease; aneurysm; ectasia.

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We appreciate the detailed and insightful commentary emphasizing the significance of coronary artery aneurysms (CAA) and coronary artery ectasia (CAE) in the context of coronary artery disease (CAD). The observations made by the authors provide a valuable contribution and expand upon a domain that is indirectly related to the focus of our study. We are responding to the commentary on our article "Long-term outcomes of myocardial revascularization in patients with multivessel coronary artery disease and comorbid pathology" [1].

CAA and CAE represent rare but clinically significant conditions characterized by localized or diffuse dilation of the coronary arteries, exceeding the diameter of adjacent normal segments or the largest coronary artery diameter by 1.5 times [2]. Despite their relatively low prevalence, these conditions may lead to severe cardiovascular complications, including thrombosis, myocardial infarction, and arterial rupture [3, 4]. The outcomes of revascularization in this patient group depend not only on the degree of coronary obstruction but also on structural abnormalities of the coronary artery. In this regard, early diagnosis and the development of individualized treatment strategies can significantly improve prognosis and reduce the risk of complications.

Although invasive assessment of CAA and CAE is primarily based on coronary angiography, advanced imaging modalities such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), coronary computed tomography (CT), and multidetector computed tomography (MDCT) provide detailed visualization of coronary artery involvement, facilitating better treatment strategy selection [4]. It should be noted that research on patients with CAA and CAE remains limited, mainly comprising case reports, case series, and a few registries [4, 5]. Furthermore, there are no definitive guidelines for the pharmacological and interventional management of patients with CAA and CAE.

The choice between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with CAA and CAE requires a thorough assessment of coronary anatomy, thrombosis risk, and the patient's clinical status. CABG is preferred for patients with large aneurysms or multiple lesions, whereas PCI may be an effective strategy for localized lesions [4]. In this regard, further studies are necessary to establish more precise recommendations for the selection of optimal treatment strategies for this patient population.

CAA and CAE were not included or considered in our study; however, their potential impact on revascularization outcomes warrants attention and further investigation. The integration of CAE/CAA-specific variables into studies assessing revascularization outcomes may provide a more comprehensive understanding of their influence.

We are grateful to the authors for their thoughtful commentary and appreciate the opportunity to engage in this discussion. Although our study did not specifically address these anomalies, we acknowledge their importance as potential modifiers of revascularization outcomes. Further research integrating the unique pathophysiological aspects of CAE/CAA into CAD studies is essential for optimizing treatment outcomes in this complex patient population.

Autor Contributions: Conceptualization, M. A. A., M. I. M. and A. Y. G.; writing – original draft preparation, M. I. M.; writing – review and editing, M. A. A., M. I. M. and A. Y. G. All authors have read and agreed to the published version of the manuscript.

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Immune Response in Obesity and Type 2 Diabetes

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Abstract

Obesity is a widespread chronic inflammatory disease that can lead to increased health risks and subsequent development of prediabetes and type 2 diabetes. The World Obesity Federation (WOF) predicts that the global number of obese adults will reach 1 billion by 2030. The World Obesity Federation (WOF) identifies Kazakhstan as a high-risk country for obesity. By 2030, obesity rates in Kazakhstan are expected to rise to 25.7% in men, 29% in women, and 9.5% in children aged 5 to 19. Kazakhstan's National Center for Public Health has observed a significant increase in overweight and obesity rates, particularly among children. Epidemiological data indicate that boys have a higher obesity rate than girls. Specifically, 23.6% of boys were classified as overweight, including obesity, compared to 17.6% of girls. Recent studies highlight the role of immune cell function in obesity-related inflammation providing a potential new target for treating obesity-linked inflammatory diseases. This review article discusses the role of immune cells in regulating obesity-related diseases, including diabetes.

Keywords: obesity, inflammation, type 2 diabetes, immune response, cytokines, T cells, B cells.

Introduction

Obesity is a multifaceted, complex illness that impairs health as excess body fat builds up. Chronic adipose tissue inflammation and the abnormal accumulation of fat deposits in the adipose tissue, liver, muscle, and pancreas triggers metabolic disorders that lead to an increased risk of diseases such as cardiovascular diseases, cancer, and type 2 diabetes mellitus (T2D). According to the World Obesity Federation (WOF), the prevalence of obese individuals in the world will increase to 1 billion adults by 2030. The WOF includes Kazakhstan as a high-risk country for obesity. In 2030 obesity in Kazakhstan is predicted to reach 25.7% in men, 29% in women, and 9.5% in children aged 5-19. The National Center for Public Health of the Republic of Kazakhstan has reported a significant increase in the prevalence of overweight and obesity, particularly among children. According to the results of epidemiological monitoring, the rate of obesity among boys was notably higher than that among girls. Specifically, 23.6% of boys were classified as overweight, including obesity, compared to 17.6% of girls. Additionally, 8.7% of boys were classified as obese, compared to 4.6% of girls [1, 2].

T2D is a long-term metabolic condition that seriously damages tissues and vital organs such as the liver, kidneys, heart, eyes, and other organs. Hyperglycemia, hyperinsulinemia, impaired glucose-stimulated insulin secretion (GSIS), and insulin resistance are hallmarks of T2D in individuals. Numerous studies have shown a strong correlation between obesity and T2D. Obesity is associated with increased susceptibility to multiple diseases and is estimated to contribute to 80 – 85% of the risk of developing T2D. Several factors have a substantial impact on the onset of obesity and type 2 diabetes (T2D), including insulin resistance, inflammatory cytokines production, impaired endothelial function, disturbed metabolism of fatty acids, and cellular mechanisms like mitochondrial dysfunction and endoplasmic reticulum stress [3]. Another potential risk factor for obesity and diabetes is long-term consumption of an obesogenic diet. In their study, Glavas et al. demonstrated the early effects of obesity and a high-fat diet on the function of the ß-cell in mice. According to their study, early overnutrition was found to cause weight gain, hyperinsulinemia, and the development of diabetes, particularly in male pups. Early overnutrition might lead to reduced expression of

the crucial transcription factor PDX1, which is responsible for normal pancreas development. This reduced expression leads to dysfunctional ß-cell and apoptosis [4]. Research has shown that the early effects of a high-calorie diet on beta-cell function in mice are associated with the pathophysiological conditions of being overweight and obese, along with insulin resistance [5].

Obesity is marked by the overproduction of pro-inflammatory cytokines, originating from impaired adipose tissue immune cells [6, 7]. Studies comparing adipose tissues in lean versus obese individuals have revealed variations in both the quantity and function of various immune cells. These include different types of macrophages (such as M1 and M2), subtypes of T cells (like T helper, CD8+, and T regulatory cells), natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), and B cells. In lean individuals, adipose tissue contains M2 macrophages, Th2, and T-regulatory cells that produce pro-inflammatory cytokines such as IL-10, IL-5, and interferon-γ. However, in obese individuals, adipose tissue is infiltrated with pro-inflammatory T cells and M1 macrophages, accumulating cytokines such as tumor necrosis factor α, IL-17, IL-6, and interleukin-1β (IL-1β). High cytokine production in obese individuals promotes adipose tissue remodeling, enhances energy expenditure, and impairs insulin sensitivity [8]. In their studies, Wu and Ballantyne classified inflammatory cells into two categories: Type 1 and 2. Type 1 inflammatory cells secrete interferon-gamma (IFN-γ), TNFα, IL-1β, IL-6, and IL-12 cytokines. Type 2 inflammatory cells include Th2 (T helper 2) cells, M2 macrophages, eosinophils, and innate lymphoid cells (ILC2) that release cytokines such as IL-4, IL-5, IL-10, IL-13, TGFβ [9]. McLaughlin et al. in their studies, show the connection between systemic inflammation and insulin resistance. In human obesity, an imbalance between Th-1 (pro-inflammatory) and Th-2 (anti-inflammatory) cells released from adipose tissues (visceral and subcutaneous) triggers systemic inflammation and leads to insulin resistance. High production of pro-inflammatory cytokines such as IL-6 and TNF-α in serum and tissues indicates pathologies (Figure 1). In obesity, increased levels of CRP, IL-6, TNFα and, IL-1β may serve as markers of pathological conditions [10, 11]. Here, we discuss immune cells' roles and behavior in regulating obesity and type 2 diabetes.

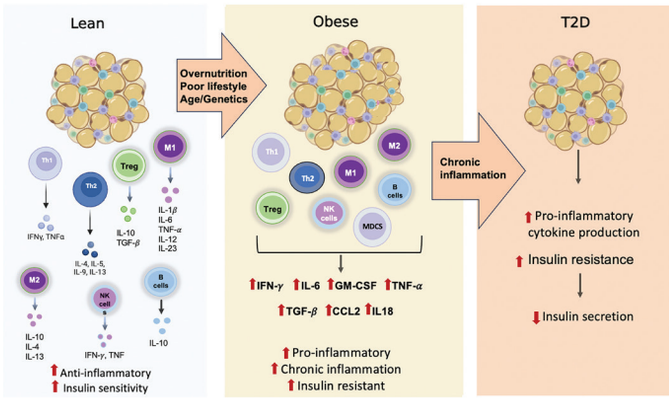

Figure 1 – Characteristics of immune cells in lean (normal), obese, and T2D conditions. In normal conditions, immune cells produce anti-inflammatory cytokines, while in obese and T2D they release more pro-inflammatory cytokines that lead to chronic inflammation, which causes insulin resistance. IL – interleukin, TGF – tumor growth factor, Th – T helper cells, Treg – regulatory T cells, IFN – interferon, TNF – tumor necrosis factor, M1/M2 – macrophages, NK – natural killer cells, MDSC – myeloid-derived suppressor cells.

Immunoregulatory cells in obesity and T2D

Macrophages

Macrophages are key components of the innate immune system that regulate immune response by releasing cytokines. Macrophages can develop unique functional traits through a process known as polarization, which is influenced by the surrounding microenvironment and the immunological context. Macrophages are divided into two distinct subtypes based on polarization: M1 macrophages (pro-inflammatory), which are classically activated, and M2 macrophages (anti-inflammatory), which are alternately activated. M1 macrophages have a strong cytotoxic ability and are immediately activated during the infection by producing pro-inflammatory cytokines. Increased levels of pro-inflammatory cytokines can result in inflammation and damage to tissues. M2 macrophages are activated to suppress inflammation by expressing anti-inflammatory cytokines and repairing tissue damage [12]. In pathological conditions, for instance, in infection and stress, the M1 macrophages produce interleukin-1β (IL-1β), IL-6, IL-12, IL-23 pro-inflammatory cytokines, nitric oxide, and tumor necrosis factor-alpha (TNF-α) as immune responses. The immunoregulatory M2 macrophages are activated release cytokines such as IL-10, and TGF-β during tissue remodeling and repair to maintain cell homeostasis. Increased levels of macrophages and accumulation in adipose tissues during obesity promote the progression of metabolic diseases including diabetes. Numerous studies reported that the pro-inflammatory macrophage accumulation in adipose tissues promotes metabolic dysfunction of cellular signaling [13]. The connection between obesity-associated inflammation and insulin resistance was made in 1993. The first well-established cytokine associated with inflammation and diabetes was TNF-α produced from the M1 macrophages [14]. Stavropoulos-Kalinoglou et al. showed regulation of inflammation using anti-TNF-α treatment increased sensitivity to insulin in rheumatoid arthritis patients with insulin resistance. The authors concluded that TNF-α can be a therapeutic target for the treatment of insulin resistance, obesity, and rheumatoid arthritis [15]. Butcher et al. found a connection between pro-inflammatory cytokine TNF-α, chemokine CCL2, and GSIS in type 2 diabetic human islets. The study found that high levels of TNF-α and CCL2 are linked to ß-cell dysfunction [16]. Thus the close connection between obesity-induced inflammation and diabetes is associated with both the failure of pancreatic ß-cells and insulin resistance in adipose and other tissues.

T Cells

T cells play a crucial role in inflammation and metabolic diseases. T cells begin their development in the bone marrow and differentiate into two distinct lineages (αβ and γδ-lineages). These lineages mature to different phenotypes of T cells that express diverse cytokines [17]. The imbalance of T cell subsets (T helper cells, cytotoxic T cells, and regulatory T cells,) in adipose and other tissues contributes to metabolic disorders [18]. Research has shown that in the case of inflammation caused by obesity, there is a significant buildup of T cells and macrophages in adipose tissue [19]. Each of the T cell subtypes expresses cytokines that regulate immune responses. During the initial phases of inflammation, pro-inflammatory cytokines like IFN-γ and TNF-α, released by various T cell subsets, such as Th1, Th17, and CD8+ cells, are essential for the disease progression.

T helper cells

T helper cells or CD4+ T cells are classified as Th1, Th2, Th17, and regulatory T cells (Treg) play a key role in regulating

the immune response. They express a wide range of cytokines for instance, Th1 produces IFN-γ, IL-4, IL-5, IL-13 from Th2, Th17 cells release IL-17, IL-21, IL-22 and IL-10 and TGFβ by Treg [20]. In metabolic syndrome and obese states, visceral adipose tissue expresses more pro-inflammatory cells, which indicates a typical shift towards a more Th1-dominated response, contributing to chronic inflammation [19, 20]. By differentiating into several subtypes, several cytokines by differentiating into several subtypes, which play a distinct role in inflammation and metabolic regulation. For instance, Th1 cells produce cytokines such as IFN-γ and TNF-α, which can exacerbate inflammation and insulin resistance [21]. Hotamisligil et al, in their study, first suggested that TNF-α is overexpressed in metabolic syndrome and obesity observing a positive correlation between insulin resistance and TNF-α level [22]. Thus, overexpression of TNF-α decreases insulin sensitivity, leading to elevated insulin levels. Uysal et al. also observed that neutralization of these cytokines can reverse insulin resistance and lower insulin levels [23].

Furthermore, it is essential to comprehend the role of CD4+ T cells in the development of insulin resistance. Recent studies have highlighted the important role of adipocytes as cells that present antigens within the immune system. Adipocytes were traditionally not considered part of the immune response; however, in obesity, they can release major histocompatibility complex (MHC) class II molecules. This expression enables them to present antigens to CD4+ T cells [24]. This capability suggests that adipocytes are not passive fat-storing cells but active participants in the immune dynamics of adipose tissue. They can modulate the activity of CD4+ T cells, potentially influencing the progression of inflammation and insulin resistance [22]. The interaction between adipocytes and CD4+ T cells highlights the complex feedback loops between metabolism and immunity in obese adipose tissue. For example, adipocytes can influence the differentiation and function of T cells through the secretion of adipokines and the presentation of antigens. This crosstalk is crucial for understanding how chronic inflammation is sustained in obesity and how it can be targeted therapeutically.

Cytotoxic T cells

CD8+ T cells are typically known for their role in cytotoxic immune responses against infected or malignant cells [25]. However, in the case of obesity, these cells accumulate in adipose tissue not in response to infection, but as part of an inflammatory reaction to excess nutrients and adipocyte hypertrophy [26]. This process is mediated by various chemokines and adhesion molecules expressed by adipose tissue under stressed conditions. The recruitment of CD8+ T cells is often preceded by changes in the adipose tissue environment, triggered by nutrient overload, which leads to adipocyte dysfunction and death. The presence of CD8+ T cells stimulates the polarization of macrophages to the M1 pro-inflammatory state [27]. This is critical as M1 adipose tissue macrophages are associated with the secretion of inflammatory cytokines, further contributing to the inflammatory environment within adipose tissue. Wang et al. highlighted that the number of CD8+ T cells is significantly elevated in the adipose tissue of both diet-induced and genetically obese mice [28, 29]. The study notes that CD8+ T cells are among the first immune cells to infiltrate the adipose tissue during the development of obesity. Their presence precedes that of macrophages, which are also key players in adipose tissue inflammation. Once in the adipose tissue, CD8+ T cells become activated and exert their effects by producing additional cytokines including IFN-γ and TNF-α, further exacerbating local inflammation. The depletion of CD8+ T cells in experimental interventions using neutralizing antibodies, have decreased adipose tissue macrophage infiltration, decreased inflammation in adipose tissue, and regenerated insulin sensitivity in obese models.

Interestingly, the study by Ahrendsen et al. reported a significantly higher presence of CD8+ T cells in the hypothalamic regions, specifically the median eminence/arcuate nucleus (ME/Arc) and the bed nucleus of the stria terminalis (BNST), of obese individuals compared to their non-obese counterparts. This was not observed in other brain regions or hypothalamic nuclei, indicating a targeted inflammatory response associated with metabolic regulatory centers. Along with the increased presence of CD8+ T cells, there was a notable rise in markers indicating cellular damage, such as activated caspase 3 and poly-ADP ribose, found in the ME/Arc of patients with obesity. This suggests that CD8+ T cells may not only be markers of inflammation but also active participants in causing neuronal damage within the hypothalamus, potentially disrupting crucial metabolic processes regulated by this area [30].

Regulatory T cells

Regulatory T cells (Treg) represent a specialized group of CD4+ T cells responsible for upholding peripheral tolerance and suppressing antigen-specific immune responses by producing TGF-β, IL-10, and IL-4 cytokines. Tregs, which are generally anti-inflammatory, are found in reduced numbers in obese conditions, further tipping the balance towards pro-inflammatory pathways. This imbalance not only perpetuates adipose tissue inflammation but also impairs insulin signaling in visceral adipose tissue and liver, promoting the progression of T2D. Treg cells represent a key type of immune cell found in visceral adipose tissue (VAT). Studies have shown that Treg cytokine production levels depend on physiological conditions. In normal conditions, the levels of Treg cells are elevated, while in diet-induced obesity, their reduction is found in VAT. The production of Treg cells in VAT is decreased by 80–90% in obese mice. Li et al. demonstrated that diet-induced obesity or long-term high-fat diet feeding inhibits the nuclear receptor PPARγ, which regulates Treg expression in VAT. Lack of PPARγ expression in mice causes a reduction in Treg cell expression that may lead to impaired anti-inflammatory activity. Reduced Treg levels have a positive effect on diabetes development and related complications. However, the exact molecular mechanisms explaining how Tregs protect against diabetes are not fully understood. The impairment of insulin production is closely linked to alterations in the immune system. The primary factors contributing to inadequate insulin release are the attack on ß-cells by Treg cells, CD8+ T cells and macrophages which release pro-inflammatory cytokines, as well as the assault on ß-cells by B cells and Th cells. In their meta-analysis, Qiao et al. found that elevated levels of pro-inflammatory cytokines (IL-6 and TNF-α) and reduced levels of the anti-inflammatory cytokine IL-10 in individuals with T2D may inhibit Tregs and the ratio of Tregs to Th1 and Th17 cells [31–34].

B cells

B cells are an important part of the adaptive immune system, primarily known for their roles in antibody production, antigen presentation, and cytokine secretion. These functions enable B cells to modulate other immune cells and influence inflammatory responses. In the context of obesity, B cells undergo significant changes that exacerbate the inflammatory environment. Such chronic immune activation is a hallmark of obesity and sets the stage for various complications, including insulin resistance and T2D. B cells accumulate in adipose tissue, particularly visceral fat surrounding internal organs. This accumulation is associated with several detrimental processes via

pro-inflammatory cytokine production, autoantibody production, and impact on T cell activation in adipose tissue. B cells in obese adipose tissue are known to produce pro-inflammatory cytokines such as TNF-α and IL-6. These cytokines contribute to the inflammatory milieu of obese adipose tissue, which can exacerbate insulin resistance, a precursor to T2D. Zhai et al. observed a B cell-mediated immune response in both obese non-diabetic and obese diabetic individuals. The results showed that B cells in both cases release pro-inflammatory cytokines such as IL-6 and TNF-α. However, the study found that obese diabetics experienced dysregulation of the immune suppression capacity of regulatory IL-10 cytokines, which is mediated by regulatory B cells [31, 35]. Moreover, B cells can produce autoantibodies that react with self-antigens in adipose tissue. This autoimmune-like response further fuels inflammation, which can impair the normal function of insulin, leading to insulin resistance and, eventually, diabetes. B cells also influence the function of T cells in adipose tissue by presenting antigens and secreting cytokines that promote T-cell activation, leading to a pro-inflammatory response. This T cell activation contributes to the systemic inflammation observed in obesity. Additionally, while B cells from obese subjects without diabetes were able to maintain some regulatory functions via IL-10 production, B cells from diabetic patients showed an impaired ability to produce this anti-inflammatory cytokine, even when stimulated. IL-10 is vital for controlling immune responses and its deficiency could lead to unchecked inflammation, further complicating metabolic dysregulation in diabetic patients [36]. One of the most critical findings from the studies conducted is the impaired antibody response to new antigens in obese diabetic patients. Despite an overall increase in antibody production, these individuals showed a reduced ability to generate antigen-specific antibodies. This was evident from their response to the influenza vaccine, where obese diabetic subjects had significantly lower increases in specific antibodies compared to non-diabetic obese subjects. This phenomenon suggests a defect in the adaptive immune response, where despite high overall B cell activation, the specificity of the immune response is compromised [36, 37]. This could potentially lead to an inadequate immune defense against new pathogens, while also contributing to chronic tissue inflammation seen in metabolic disorders.

Myeloid-Derived Suppressor Cells (MDSC)

Epidemiological studies have demonstrated that obesity changes some immune cell phenotypic and functional characteristics. Pathologically activated neutrophils and monocytes are called myeloid-derived suppressor cells (MDSCs) with strong immunosuppressive properties. The common myeloid progenitor (CMP) is a varied group of immature myeloid cells found in the bone, capable of differentiating into myeloid-derived suppressor cells (MDSCs). In mice, this process also occurs in the spleen. MDSC cells are classified into two groups, monocytic (M-MDSC) and polymorphonuclear/granulocytic (PMN-MDSC) that regulate immune response via different cellular mechanisms by producing immune suppressive cytokines. Accumulation of MDSC cells in obesity induces suppression of T-cell activation, preventing NK cell cytotoxicity, and polarizing macrophages toward a tumor-promoting phenotype. These types of cells are well-studied in tumor development and chronic inflammatory diseases in obese individuals [38–40]. Despite some advancements, our understanding of the roles and unique characteristics of these cells in individuals with T2D remains limited and requires further research.

Natural Killer (NK) Cells

Natural Killer (NK) cells are a type of innate lymphocyte that can quickly react to infected or altered cells without needing prior activation, releasing destructive substances like perforins or granzymes. They primarily kill target cells through cytotoxic activity, however, they contribute to immune regulation by releasing substantial levels of pro-inflammatory cytokines and chemokines, including TNF, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Moreover, these characteristics show their difference from T and B lymphocytes. Numerous studies demonstrate the frequencies of NK cells are decreased in individuals with excess weight, which relates to insulin resistance. However, some studies found that the frequencies of NK cells did not change during obesity [32, 41]. Therefore, the structural and functional properties of these cell groups in obesity are still unknown and need more studies.

Conclusion

Obesity and its health consequences are increasing global problems. The obesity phenomenon is characterized not only by an elevation in body mass due to high levels of fat deposits but also by a low-level chronic inflammatory response caused by the expression of inflammatory adipokines (for instance, leptin, MCP-1) from adipose tissue and molecular mediators of inflammation (e.g., IL-1β, IL-8, IFN-γ, and IL-17). The chronic, low-grade inflammatory process in excessive body mass triggers chronic damage/inflammation that systemically affects the entire body and stimulates an increase in immune cell density within the bloodstream, contributing to the development of many metabolic diseases, including T2D. The role of immune regulatory cells in the context of obesity, their phenotypic characteristics, and their underlying mechanisms of action still need further investigation. Research on immunoregulatory cells will enable a more profound comprehension of the cellular processes involved in disease progression and potentially provide for earlier diagnosis of obesity-related diseases.

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The Incidence of Pharyngeal Cancer in the Republic of Azerbaijan for 2019–2022

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Abstract

Introduction: Pharyngeal cancer is a rapidly progressing disease that leads to disability. Epidemiological studies are one of the components of the anti-cancer measures. Knowledge of the territorial prevalence of tumors allows us to solve the issues of their prevention and early detection.

The **aim** of the present study was Epidemiological analysis of the incidence of pharyngeal cancer in the Republic of Azerbaijan.

Methodology: The analysis of the epidemiological situation was carried out using incidence rate, attack rate and age-standardized rate per 100.000 population from 2019 to 2022 in the Republic of Azerbaijan

Results: The incidence rates of pharyngeal cancer in the Republic of Azerbaijan for the period 2019–2022 were varied in the range 1,0–1,2 (men) and 0,5–0,7 (women). A similar case was observed in attack rates which were 4,9 -5,7 in males, 3,2- 3,5 in females. The highest values of the standardized rates of the incidence of pharyngeal cancer were observed in the age group of 50–59 years and 60–69 years for both sex.

Conclusion: The incidence of pharyngeal cancer remained stable over the study period. The incidence of this form of cancer was relatively higher among men than among women.

Keywords: pharyngeal cancer, morbidity, incidence rate, attack rate, age-standardized rate.

Introduction

Cancer of the mucous membrane of the oral cavity and oropharynx account for up to 3.5% of the total cancer incidence. Since the 80 s of the last century, there has been a steady increase in the incidence of this pathology. The cancer growth aggressiveness in this localization, the high frequency of local and distant metastases leads to high rates of one-year mortality and low long-term survival in these patients [1]. All of this makes this problem one of the urgent problems of modern oncology.

The mucous membrane of the oral cavity and oropharynx, and the underlying tissues, represent an anatomically complex area and determine the specificity of the clinical course and treatment of cancer developing here. Among malignant tumors of the head and neck, cancer of the oral cavity and oropharynx ranks second in frequency after cancer of the larynx. The overall five-year survival rate in patients with cancer of the oral mucosa and oropharynx in stages I-II is up to 45%, but in stage III it reaches no more than 30%. At stage IV of the process, the chances of a long-term recovery from the cancer process are almost minimal. The survival rate for this tumor prevalence is only about 5-11% [2, 3].

Pharyngeal cancer almost always occurs in the squamous cell form. The following variants are rarely observed: basaloid squamous cell carcinoma, undifferentiated carcinoma. In recent decades, the incidence of HPV-related squamous cell carcinoma in the oropharynx has increased 3-4 times, while the incidence of HPV-negative squamous cell carcinoma in the oropharynx has decreased 2 times [4, 5].

Although pharyngeal cancer is traditionally considered a disease of adults, it occurs at a younger age than other squamous cell carcinomas of the head and neck and has a bimodal age distribution. Recently, there has been an increase in the incidence of pharyngeal cancer at a young age, and approximately 6% of this disease is detected before the age of 45 years.In some parts of the world, 20% of pharyngeal cancer cases (especially in men) are detected before the age of 30.

In the United States, pharyngeal cancer is approximately 20 times more common in African Americans than in white-skinned young adults. Pharynx cancer is observed 4-5 times more often in men than in women [4, 6].

It has been noted that smoking and the use of other tobacco products increases the risk of developing pharyngeal cancer, especially carcinoma of the oropharynx and hypopharynx. Excessive alcohol consumption can increase the risk of developing pharyngeal cancer by up to 10 times [7–9]. Dietary factors, especially the consumption of salty foods, are also thought to play a role in the development of pharyngeal cancer [10]. Recently, a lot of evidence has accumulated that there is a definite connection between human papillomavirus (HPV) and pharyngeal cancer. A high risk of developing pharyngeal cancer is also associated with immunodeficiency [11, 12].

Based on the above, the aim of this study was to research the incidence of pharyngeal cancer in the Republic of Azerbaijan for the period 2019–2022.

Materials and methods

The epidemiological situation of the incidence of pharyngeal cancer in the republic was assessed on the basis of statistical data from the National Center of Oncology and statistical reporting forms No. 7 of the Ministry of Health of the Republic for the period 2019–2022. The following indicators were used as analysis indicators: extensive percentage rate among other types of cancer (in %), incidence rate (per 100.000 population), attack rate (per 100.000 population) and age-standardized rate (per 100.000 population). These values are calculated according to the methods used in oncology, as well as according to the method recommended by WHO for quantitative assessment of health status.

Results. Study revealed that in the structure of the incidence of cancer in the population of the republic, pharyngeal cancer during the studied period was insignificant and in terms of the percentage rate varied in the range of 0.8–1.1% in males and 0.4–0.6% in females, and the highest extensive indicator was noted in 2020, both in males (1.1%) and females (0.6%). It should be noted that the incidence rates are higher (3.9 times) in males compared to females (Figure 1)

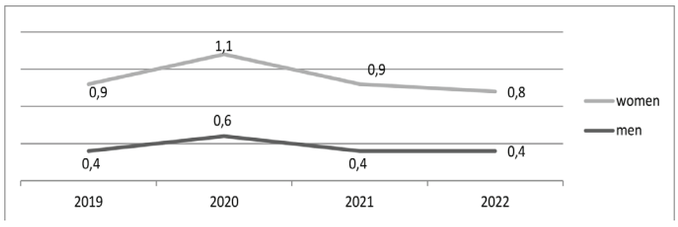

Figure 1 – Percentage rates of pharyngeal cancer in the structure of the incidence of cancer in the Republic of Azerbaijan for 2019–2022 (%)

Incidence is a measure of a disease that allows us to determine the probability of the number of new cases of a disease being diagnosed during a given period. The calculation of the intensity indicator revealed fairly stable values of this indicator for the studied period, both in males, the range was 1,0–1,2 (per 100.000) and in females, this value ranged from 0.5 to 0.7 (per 100.000) The highest level of this indicator was noted, as in the case of the extensiveness indicator, in 2020 for both males (1.2 per 100.000) and females (0.7 per 100.000). A higher incidence rate (1.9 times) was found in males compared to females (Figure 2).

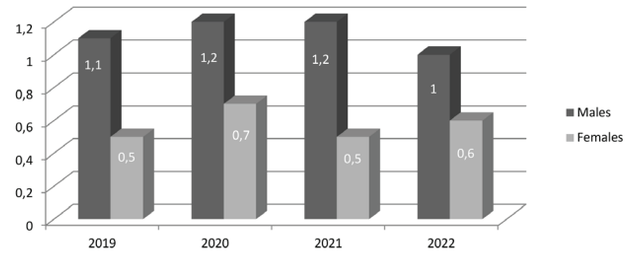

Figure 2 – Incidence rates of pharyngeal cancer in the Republic of Azerbaijan for 2019–2022 (per 100.000)

Attack rate (or prevalence) is a measure of disease that allows us to determine a person's likelihood of having a disease. Therefore, the number of prevalent cases of pharyngeal cancer is the total number of cases of this type of cancer existing in a population.

The range of attack rate was 4.9 -5.7 (per 100.000) in males, and in females – 3,2–3,5 (per 100.000). The highest attack rate was noted in 2022 for both males (5.7) and females (3.5). A higher incidence rate (1.7 times) was found in males compared to females (Figure 3).

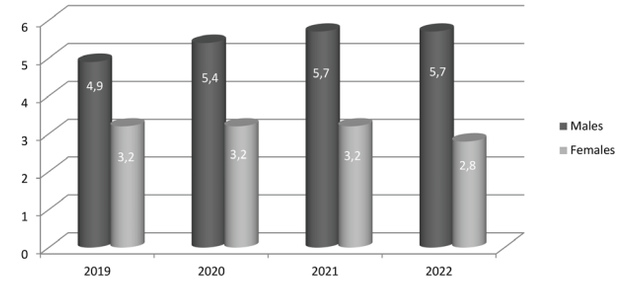

Figure 3 – Attack rates of pharyngeal cancer in the Republic of Azerbaijan for 2019–2022 (per 100.000 population)

Comparisons of incidence rates between time periods are usually more representative if differences in the age structure of the populations are taken into account. This is especially true if the disease being observed varies with age. Age-standardized rates are often used to make such comparisons in oncology because they take into account differences in cancer incidence in the age structure of the populations being compared. Based on this, age-standardized indicators for 2019 and 2022 were calculated to assess the overall incidence of pharyngeal cancer in the Republic of Azerbaijan (Tables 1 and Table 2).

As shown in Table 1, the incidence of pharyngeal cancer in 2019 in the age group 0–17 years was not detected. The lowest values of this incidence were observed in the age group of 18–29 years and 30–39 years in both males – 0.02 and females – 0.02. Starting from the age group of 40–49 years, there is an increase in the incidence of both males (0.3) and females (0.1), reaching a peak in the age group of 50–59 years (0.4) in the case of males and 60–69 years (0.2) – in the case of females. The value of the standardized indicator, regardless of age, was 1.1 for males and 0.5 for females with an excess of 2.2 times.

The values of the age-standardized incidence rate of the population with pharyngeal cancer in 2022, presented in Table 2, also indicate an increase in incidence. The lowest values of this indicator were found only in females, in the age group 0–17 years (0.02).

Table 1 Age-standardized incidence of pharyngeal cancer in the Republic of Azerbaijan for 2019 (per 100.000)

Years	Incidence (per 100 000)		Average standard		Standardized indicator (per 100 000)	
	males	females	males	females	males	females
0–17	-	-	28135,3	24411,2	-	-
18–29	0,1	0,1	20092,1	18804,8	0,02	0,02
30–39	0,1	0,1	16951,7	17262,1	0,02	0,02
40–49	2,3	0,8	12424,2	13100,5	0,3	0,1
50–59	3,1	1,0	12263,5	13626,3	0,4	0,1
60–69	4,1	2,5	6862,1	8033,3	0,3	0,2
70 >	3,1	1,3	3271,1	4761,8	0,1	0,06
	1,1	0,5	100000	100000	1,1	0,5

Table 2 Age-standardized incidence of pharyngeal cancer in the Republic of Azerbaijan for 2022

Years	Incidence (per 100 000)		Average standard		Standardized indicator (PER 100 000)	
	males	females	males	females	males	females
0–17		0,1	27858,6	24217,4		0,02
18–29	0,1	0,5	18681,9	17106, 0	0,02	0,08
30–39	0,2	0,3	17354,3	17732,9	0,03	0,05
40–49	0,9	0,6	12689,0	13220,7	0,1	0,08
50–59	3,9	1,5	11947,5	13390,8	0,4	0,2
60–69	3,0	1,3	7922,7	9231,5	0,2	0,1
70 >	6,1	1,2	3546,0	5100,7	0,2	0,06
	1,0	0,6	100000	100000	0,9	0,6

This is followed by an increase in incidence, the peak level occurs in the age group 50–59 years, both in males (0.4) and in females (0.2), with a subsequent decrease towards the age group 70 >, both in males (0.2) and in females (0.06). The value of the standardized indicator, regardless of age, was 0.9 for males and 0.6 for females.

Discussion

Cancer is the leading cause of death and loss of life expectancy in every country in the world. According to the World Health Organization (WHO) 2019 estimates, cancer is the first or second leading cause of death under age 70 in 112 of 183 countries, and the third or fourth leading cause in another 23 countries. Rising cancer mortality comes amid declining stroke and coronary heart disease mortality rates in many countries [1–3].

Oral cavity and pharyngeal cancer is the sixth most common cancer in the world. Due to widespread tobacco and alcohol use worldwide, oral cavity and pharyngeal cancer (OPC) incidence rates are increasing every year. The estimated annual incidence is about 275,000 for oral cavity cancer and 130,300 for pharyngeal cancer, excluding the nasopharynx, with two-thirds of these cases occurring in developing countries [6–8].

Our study analyzed the incidence rates of pharyngeal cancer in the Republic of Azerbaijan. In the structure of malignant neoplasms incidence in the population of the republic, pharyngeal cancer for the period 2019–2022 was in 9–10 places and in terms of percentage among other types of cancer varied in the range of 0.8% – 1.1% in males and 0.4–0.6% in females. The results of the study showed a slight increase in them during the study period, the values of which varied in men in the range of 1.0–1.2, and in women and 0.5–0.7.

In many countries, the incidence of pharyngeal cancer in men is several times higher than in women. Increased incidence of oropharyngeal cancer was observed both in middle-aged men (40–59 years) and in older men (≥60 years). In Republic of Azerbaijan, the highest values of age-standardized incidence rate of pharyngeal cancer in men were noted in the age group of 50–59 years (0.4), and in women in the group of 60–69 years 0.2.

Thus, the results of the analysis of the situation on pharyngeal cancer in the Republic of Azerbaijan can form the basis for the development of primary and secondary prevention of this type of cancer among the country's population.

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The Role of Activation of the Tryptophan-Kynurenine Axis in the Pathogenesis of Acute Cerebrovascular Diseases: A Literature Review

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Abstract

Introduction: Acute cerebrovascular disorders are a major contributor to adult disability. The underlying processes that contribute to their development include inflammation, excitotoxicity, oxidative stress, and dysregulation of the tryptophan–kynurenine pathway, which is essential for neuronal survival. However, the precise mechanisms and significance of these processes are not fully comprehended, and their influence on the efficacy of therapeutic approaches remains uncertain.

The aim of this study is to investigate the role of the tryptophan-kynurenine metabolic pathway in the development of stroke and its potential as a biomarker and therapeutic target.

Results and Conclusions: Tryptophan metabolism primarily occurs through the kynurenine pathway. Among its metabolites, kynurenine, kynurenic and choline acids are the most significant. Them have both neuroprotective and neurotoxic effects. Activation of the kynurenine pathway is linked to chronic inflammation, increasing the risk of cardiovascular and neurodegenerative conditions. Kynurenic and choline acids regulate N-methyl-D-aspartate receptor activity and oxidative stress. The increased production of choline and 3-hydroxyanthranilic acid due to oxidative stress is a major mechanism of neuronal damage under ischemic. The regulation of the balance between the neuroprotective and neurotoxic properties of metabolites produced by the kynurenine pathway is essential for normal brain function.

Keywords: Cerebrovascular Disorders, Kynurenine, Tryptophan, Inflammation, Oxidative Stress, NMDA Receptors.

Introduction

Acute cerebrovascular events, including ischemic strokes, are characterized by a sudden onset of neurological impairment due to reduced blood flow to the brain or bleeding in the brain. The underlying mechanisms involve a complex interplay of inflammatory responses, glutamate toxicity, oxidative stress, and metabolic imbalances, particularly in regard to the tryptophan-kynurenine pathway [1].

The data from the studies conducted demonstrate that levels of metabolites in the kynurenine pathway, including kynurenine (KYN) and kynurenic acid (KYNA), vary in patients with cerebrovascular disorders. Elevated levels of KYN and related metabolites have been associated with the severity of atherosclerosis and other cardiovascular conditions, which are risk factors for stroke [2, 3].

Furthermore, a metabolic analysis of blood samples has revealed a significant correlation between plasma levels of tryptophan (TRP) metabolites and indicators of inflammation and oxidative stress in patients with stroke [4]. These findings support the idea that alterations in the kynurenine pathway may serve as both biomarkers and potential treatment targets for acute cerebrovascular disorders.

The KYN pathway has received significant attention due to its potential for therapeutic applications in various neurological and mental health conditions, particularly in relation to acute cerebrovascular disorders. Preclinical research has demonstrated that manipulating the KYN pathway may provide an effective treatment option for patients with limited therapeutic alternatives, highlighting the importance of ongoing research in this field [5].

Therefore, the question remains unanswered: what is the role of the activation of the tryptophan-kynurenine pathway in the pathogenesis of acute cerebrovascular disorders.

The aim of this study was to investigate the effect

of alterations in the kynurenine metabolic pathway on the key pathogenic mechanisms underlying acute cerebrovascular disease, and to explore the potential use of pathway components as biomarkers and therapeutic targets for acute cerebrovascular therapy.

To conduct this literature review, two researchers independently carried out a comprehensive analysis of scientific publications published in peer-reviewed journals and scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Each publication was evaluated based on the following criteria: transparency and validity of research methodology, amount of experimental data, statistical significance of results, representativeness of study sample (in case of clinical trials), and correctness of data interpretation. A total of 21 review articles and 3 case-control studies were included in the analysis. Additionally, 1 Mendelian randomization trial, 3 experimental studies, and 1 cohort study were considered. A comparative analysis of literature sources is presented in Supplementary File, Table 1.

Table 1 Comparative analysis of the original research used in the literary review.

Acute ischemic stroke (AIS), significant carotid artery stenosis (SCAS), kynurenine (KYN) pathway (KP), tryptophan (TRP), 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), quinolinic acid (QA), picolinic acid (PA), kynurenic acid (KA), anthranilic acid (AA), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), melatonin (MEL), tryptamine (TA), neopterin (NEO), KTR: 1000 × [KYN]/[TRP], oxidative stress (OS), malondialdehyde (MDA), riboflavin (RBF), liquid chromatography–tandem mass spectrometry (LC-MS/MS), high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), trauma brain injure (TBI), late-life depression (LLD), healthy controls (HC), Mental Disorders (MD), cardiovascular disease (CVD)

Source	Type of research	Methodology description	People/ animals	N	Mean age, years	Sex female/ male	What was measured	Method	limitations
Hajsl, 2020[1]	Case-control	+	people	25 SCAS, 18 AIS, 25 HC	70 (59.0–78.6) SCAS/ 71 (46.8–82.6) AIS / 59 (38.2–65.0) HC	8/17 SCAS / 11/7 AIS / 11/14 HC	KP and serotonin pathway metabolites (TRP, KYN, 3-HK, 3-HAA, KA, AA, QA, PA, 5-HT, 5-HIAA, MEL), TA, markers of inflammation (NEO, KTR), OS marker MDA, and RBF	LC-MS/MS	Small number of probands in studied groups; no information about dietary habits
Genestet, 2014[2]	Analysis of kynurenine production of cultured P. Aeruginosa strains.								
Yan, 2015[3]	Case-control	+	people	28 severe TBI/ 11 patients undergoing elective neurosurgery for implantation of ventriculo-peritoneal shunts following a diagnosis of hydrocephalus (controls) and 20 healthy controls	35 (21-69) TBI; 52 (30-74) controls; 38 (21-55) healthy controls	6/22 TBI; 5/6 controls; 12/8 healthy controls	TRP, KYN, KA, QA, AA, 3HAA	HPLC and GC-MS	no commercially available antibody for the dephosphorylated/ inactive form of IDO1 to allow for its detection in situ; the limited number of tissues stained and the variety of brain regions analysed.
Wu, 2018[4]	Case-control	+	people	156 LLD (85 with MD, 71 without MD)/ 129 HC	66.38±7.34 LLD with MD / 66.78±6.99 LLD without MD / 67.08±6.86 HC	65/20 LLD with MD / 49/22 LLD without MD / 91/38 HC	TRP,KYN, KYNA	LC-MS/MS	the neurotoxic KYN metabolites (QUIN) were not measured.
Ramírez-Ortega, 2017[5]	experimental	+	Animals (rats)	Assessed the impact of 3-hydroxykynurenine and 3-hydroxyanthranilic acid on copper toxicity in astrocyte cell cultures.					
Zuo, 2016[6]	Cohort study	+	people	7,010	Age group 46-49 – 52.8%; age group 70-74 – 47.2%	55.3%/44.7%	KYN, TRP, NEO, KA, 3-HK, 3-HAA, QA	LC-MS/MS	Information on CVD and diabetes at baseline may have been subject to misclassification due to the reliance on self-reporting. The study cohort was from a small geographical area representing 2 narrow age groups.
Wang, 2023[7]	experimental	evaluation of the effect of 3-hydroxykynurenine and 3-hydroxyanthranilic acid on copper toxicity in rat astrocyte cells using cell culture and cell viability analysis techniques.							
Li, 2020[8]	Mendelian Randomization study	+	people	6056 Twins UK cohort, 1768 KORA F4 study	53.4 Twins UK cohort, 60.8 KORA F4 study	92.9% female Twins UK cohort, 51.5% female KORA F4 study	TRP, 5-HT, KYN	genome-wide associations	findings, largely in Europeans, may not be applicable to other populations; No SNPs for serotonin were genome-wide significant, which may bias toward the null in two-sample MR; a Bonferroni correction to account formul tiple comparisons may increase type 2 error

Tryptophan Metabolism

TRP is an essential amino acid that performs many functions in the body, including acting as a precursor to key neurotransmitters such as serotonin and melatonin. About 95% of tryptophan is degraded, mainly through the kynurenine pathway, while the remaining 5% is converted to serotonin through tryptophan hydroxylase (TPH) [2, 6].

The kynurenine pathway (Figure 1) is an essential metabolic process that begins with the breakdown of TRP and leads to the formation of several neuroactive metabolites, such as KYN, KYNA and quinolic acid (QA) [7]. The initial stage of the KYN pathway is catalyzed by enzymes such as indolamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). These enzymes lead to the formation of N-formyl-l-kynurene, which is then converted to KYN. [2]. KYN can be converted into KYNA through the action of kynurenine aminotransferases I (KAT I), II, and III, which are primarily expressed in astrocytes and are responsible for the majority of KYNA biosynthesis. KYNA exerts a neuroprotective effect by acting as an antagonist at N-methyl-D-aspartate (NMDA) receptors, α7n-nicotinic acetylcholine receptors (α7n-nAChRs), and, at higher concentrations, also acts as a weak antagonist at α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainate receptors [5], thereby mitigating excitotoxic effects and regulating neurotransmitter levels [8]. In turn, QA promotes the synthesis of nicotinamide adenine dinucleotide (NAD+), which is essential for energy metabolism and plays a significant role in inflammatory responses [2].

It is generally accepted that TRP is converted to QA in microglial and macrophage cells, or to KYNA in astrocytic cells. Depending on the activity of these metabolites, this process is considered neuroprotective in astrocytes, but neurotoxic in microglial and macrophage cell types, leading to a dualistic perspective on its role in disease [8]. QA is an important product of the kynurenine pathway that contributes significantly to neuronal cell death and chronic dysfunction via at least nine distinct mechanisms, including the generation of reactive oxygen species (ROS), compromised blood-brain barrier (BBB), glutamate-induced excitotoxicity, cytoskeletal instability, mitochondrial dysregulation, stimulation of tau phosphorylation, and impairment of autophagy [9].

3-Hydroxyanthranilic acid (3-HAA) is a metabolite of the kynurenine pathway that has been recognized as a neurotoxic substance capable of inducing neuronal apoptosis. Despite this, 3-HAA has also been shown to have anti-inflammatory properties, as it can reduce inflammation caused by Th17 cells. In blood vessels, 3-HAA inhibits the uptake of low-density lipoproteins (LDL) by macrophages, thereby decreasing local vascular inflammation and the risk of atherosclerosis. Additionally, 3-HAA lowers the levels of very low-density lipoproteins and exhibits beneficial lipid-lowering properties [2].

Kynurenine metabolism and inflammation

Neuroinflammation plays a significant role in the pathogenesis of cerebrovascular disorders, with the kynurenine pathway serving as a connection between inflammation and neuronal damage [8, 10]. Inflammation is a complex process that can lead to the activation of the kynurenine pathway, which is associated with the development of chronic, nonspecific inflammation. This inflammation can exacerbate a range of conditions, including those related to the cardiovascular and neurodegenerative systems [2]. KYN has the potential to cross the BBB and affect neuronal excitability, potentially leading to neuroinflammation and neuronal damage [7]. An increased level of KYN also results in a decrease in ROS production by activated neutrophils [11].

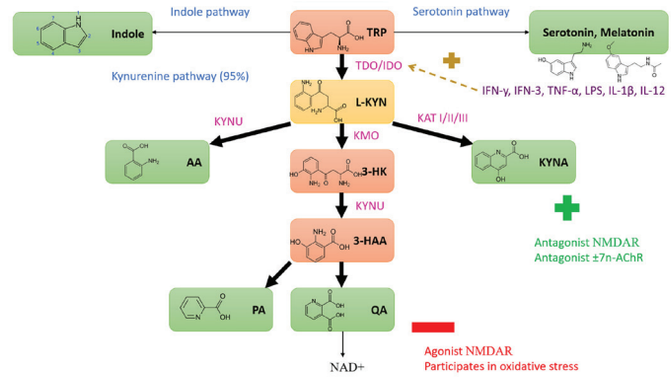

Figure 1 – TRP Metabolism and kynurenine pathway. TRP – tryptophan, KYN – kynurenine, TDO – tryptophan 2,3-dioxygenase, IDO – indoleamine 2,3-dioxygenase, IFN-y – interferon gamma, IFN-3 – interferon 3, TNF-α – tumor necrosis factor, LPS – lipopolysaccharide, IL-1β – interleukin-1 beta, IL-12 – interleukin-12, KYNA – kynurenic acid, KAT – kynurenine aminotransferase, 3-HK – 3-hydroxykynurenine, KMO – kynurenine 3-monooxygenase, AA – anthranilic acid, KYNU – kynureninase, 3-HAA – 3-hydroxyanthranilic acid, QA – quinolinic acid, PA – picolinic acid, NAD+ – nicotinamide adenine dinucleotide +, NMDAR – N-Methyl-d-Aspartate receptor, ±7n-AChR – ± α7 acetylcholine nicotinic receptor

During the acute phase of ischemic stroke, a series of inflammatory processes are initiated, leading to the activation of resident microglia and the infiltration of peripheral white blood cells into the injured brain tissue [4, 10]. This infiltration results in the release of pro-inflammatory cytokines, which enhances the internal inflammatory response of brain cells. The inflammatory mediators released by the infiltrating leukocytes can activate the kynurenine pathway, specifically its neurotoxic metabolites, leading to neuronal damage and affecting clinical outcomes [2, 4]. Pro-inflammatory cytokines may increase IDO activity, which enhances the conversion of TRP to KYN, thereby altering metabolism towards the generation of neurotoxic instead of neuroprotective substances [12, 13]. These downstream metabolites, including KYN, 3-HK, 3-HAA and QA, have been shown to induce apoptosis in various types of immune cells, including T cells, B cells, natural killer cells, and neutrophils [14]. Therefore, they help to reduce inflammatory responses. KYNA may reduce the formation of pro-inflammatory cells by regulating the immunosuppressive effects of AhR [2]. However, KYNA can also contribute to the development of vascular disease through chronic inflammation [15].

Assessment of the concentration of TRP metabolites in the blood of patients with acute cerebrovascular disorders and significant stenosis of the carotid arteries showed that patients with stenosis of the carotid artery and stroke had reduced levels of TRP and 3-HAA, as well as elevated levels of circulating AA and 3-NK [4]. Data from another study of stroke patients showed a positive correlation between the KYN/TRP ratio and the severity of the stroke [16]. As the subarachnoid hemorrhage progressed, the TRP level rose dramatically in conjunction with the development of vasospasm [6].

In the context of stroke, acute inflammation can lead to an increase in neurotoxic metabolite levels, which may affect the severity of neurological impairments and recovery outcomes [1, 8]. According to the study, patients with acute ischemic stroke showed decreased serum levels of TRP and KYNA, as well as increased levels of inflammatory biomarkers such as highly sensitive C-reactive protein (CRP) [10]. Activation of the KYN pathway has been associated with the severity of stroke, as measured by the National Institutes of Health Stroke Scale

(NIHSS). Furthermore, increased activity of IDO has been found to correlate positively with levels of CRP, suggesting a potential link between inflammation and TRP metabolism in stroke patients [10].

Kynurenine metabolism and excitotoxicity

In the context of excitotoxicity, metabolites of KYN exhibit both neuroprotective and neurotoxic effects, depending on their concentration and specific metabolic pathways activated. KYNA exhibits neuroprotective effects as it is an endogenous antagonist of NMDA receptors, which are involved in regulating neuronal excitability, synaptic plasticity, and neuroinflammation through activation by glutamate. QA, on the other hand, has the opposite effect by increasing excitotoxicity as it acts as a potent agonist for NMDA receptors, leading to their overactivation [2, 8, 17, 18] and uncontrolled release of glutamate into the synapse [19, 20]. This leads to an increase in Ca2+ influx into cells, which results in a cascade of damaging events, including the activation of pro-apoptotic pathways, mitochondrial dysfunction, and oxidative stress. This process is particularly significant in conditions of ischemia, such as stroke, where the concentration of ROS increases significantly in affected tissues, leading to cell death in the perifocal area.

The balance between these metabolites is essential for the proper functioning of neurons. Any imbalance can lead to damage to neurons and the progression of acute cerebrovascular disorders [13, 20].

Kynurenine metabolism and oxidative stress

Recent research has shown that activation of the kynurenine pathway during acute ischemia events leads to an accumulation of neurotoxic metabolites, such as QA and 3-HK, which contribute to neuronal damage and oxidative stress [2, 12]. Even relatively low levels of 3-HAA can cause neurotoxicity by inducing oxidative stress [21]. QA also contributes to oxidative stress development by participating in lipid peroxidation reactions and producing ROS [2]. KMO, located on the outer mitochondrial membrane, is the main synthetase in the QA pathway. It converts KYN to 3-HK, which then penetrates the BBB and increases the concentration of a substrate necessary for QA production. This leads to apoptosis of neurons, the generation of free radicals, and the initiation of oxidative stress in the brain, at nanomolar levels. These effects result in increased metal toxicity in astrocyte cultures, and a synergistic effect on neurotoxicity from QA [22]. PA is a non-specific metal ion chelator and neuroprotective agent that has the potential to inhibit QA-induced neurotoxicity. However, its inhibitory effect is less potent than that of KYNA [12]. When the QA level is high, microglial and neuronal NAD+ catabolic activity is limited, which in turn results in the cumulative neurotoxicity of QA in patients with recurrent major depressive disorder, as evidenced by higher levels of KYN metabolites [23]. Oxidative stress is a significant mechanism responsible for QA-induced neurotoxicity. Free radicals can activate various signaling pathways, resulting in pathological alterations in brain cells [5].

KYN has also been shown to reduce DNA and protein degradation caused by the hydroxyl radical and peroxynitrite, as well as weaken the production of ROS and lipid peroxidation induced by pro-oxidant compounds, such as iron(II) sulfate, peroxynitrite, and 3-nitropropionic acid, in rat brain homogenates [5].

Kynurenine metabolism and atherosclerosis

There is evidence suggesting increased levels of KYN, QA and KNA in the blood plasma of patients with atherosclerotic disease [24]. In addition, it has been demonstrated in an animal model of atherosclerosis that the level of IDO1 significantly increases in the blood serum during the development of atherosclerosis and correlates positively with its advanced stages [25]. This may be due to the activation of T cells and the production of IFN-γ, which results in an increase in IDO1 levels. This process leads to macrophage apoptosis and foam cell formation, thereby accelerating atherosclerosis progression. Subsequently, the process also activates AhR in macrophages, resulting in the production of ROS, which exacerbates inflammation of the vessel wall and contributes to lipid accumulation in blood vessels, ultimately leading to vascular atherosclerosis [2]. IDO1 also demonstrates a positive association with both stroke and other conditions such as coronary artery disease, diabetes mellitus, and prostate cancer [26].

The analysis of neuroprotective effects of kynurenine pathway metabolites

Therefore, the neuroprotective effects of the metabolic products of the kynurenic pathway are:

– KYNA, by antagonistically interacting with the NMDAR (reduction of excitotoxicity), a7n-nAChR (immunosuppressive effects [2]), and at higher concentrations with AMPA and kainate receptors [5], thereby reducing excitotoxicity [8], modulating cholinergic and dopaminergic transmission is important for cognitive function.

– 3-HAA, due to its anti-inflammatory and hypolipidemic properties [2].

– KYN causes neuroinflammation, damage to neurons [7], by reducing the degradation of DNA and proteins caused by hydroxyl radicals and peroxynitrites; reduces ROS and lipid peroxidation, [5]

– PA by reducing neurotoxicity of QA [12].

The analysis of neurotoxic effects of kynurenine pathway metabolites

In turn, the following metabolites of the kynurenine pathway have the potential to cause neurotoxic effects:

– KYN reduces ROS production [11].

– QA by synthesizing NAD+ for inflammatory processes [2]; QA by ROS formation, BBB disorders, glutamate-induced excitotoxicity [2, 8, 17, 18, 19, 20], cytoskeletal instability, mitochondrial dysregulation, tau protein stimulation. phosphorylation and autophagy disorders, increasing cell death in the perifocal area [9].

– 3-HAA, causing apoptosis of neurons and oxidative stress

– An increase in IDO activity changes kynurenine metabolism towards the production of neurotoxic rather than neuroprotective substances [12, 13].

– KMO, increasing the number of QA [22].

The role of the tryptophan-kynurenine axis in acute cerebrovascular diseases

The findings of the investigation indicate that TRP performs a significant function in the body by serving as a precursor for neurotransmitters like serotonin and melatonin. Approximately 95 percent of TRP undergoes degradation through the kynurenine metabolic pathway, which influences the formation of neuroactive substances such as KYNA and QA. These metabolites can potentially have either neuroprotective or neurotoxic consequences, depending on the specific cell type.

The action of metabolites produced by the kynurenine

pathway, including 3-HAA, can be neurotoxic, but they can also have anti-inflammatory and lipid-lowering effects. These findings suggest a complex relationship between TRP metabolites and the pathogenesis of various conditions, which warrants further research to elucidate the mechanisms of their actions in the body.

KYN metabolism also plays a significant role in the development of neuroinflammation, and is linked to acute and chronic inflammatory responses that affect the condition of brain tissue and neurons. Increased levels of KYN may activate neurotoxic metabolites, leading to neuronal damage and reduced production of ROS.

Research has highlighted the role of peripheral inflammation in regulating the metabolism of KYN and its systemic effects. It has been demonstrated that exercise can increase the removal of KYN from skeletal muscles, potentially decreasing its accumulation in the brain and alleviating related mood disorders [7]. This emphasizes the significance of inter-organ communication facilitated by KYN metabolites, which not only influence immune responses but also impact overall health.

In addition, the metabolism of KYN plays an important role in the regulation of the neuroprotective and neurotoxic potential of its metabolites, which affects the function of NMDA receptors and the level of excitotoxicity in neurons. Based on the specific effects that KYN metabolism has on excitotoxicity, it is possible to assume that the modulation of these metabolites could represent a potential treatment strategy for neurological diseases associated with an imbalance between neuroprotective and neurotoxic effects. Further research in this field could lead to the development of new drug therapies aimed at stabilizing the metabolism of KYN and preventing neuronal damage in conditions of increased excitotoxicity.

The data from the studies conducted indicate that activation of the kynurenine pathway may lead to neurotoxicity due to the action of certain metabolites, such as QA and 3-HK, and can cause oxidative stress within brain cells. Additionally, QA may contribute to the development of oxidative stress by activating lipid peroxidation reactions and generating ROS. At the same time, mechanisms of protection against QA-induced neurotoxicity may include non-selective metal ion chelation by reactive astrocytes and the ability of kynurenine to reduce oxidative stress within neurons.

The research findings suggest a significant elevation in the levels of KYN and its metabolites in the plasma of patients with atherosclerotic disease, which may be linked to the activation of IDO1, an increase in T cell count, and IFN-γ. Animal studies demonstrate that higher IDO1 levels in atherosclerosis induce macrophage apoptosis and formation of foam cells, thereby accelerating disease progression. Additionally, the activation of AhR in macrophages during atherosclerotic conditions leads to enhanced inflammation of the vascular wall, accumulation of lipids, and ultimately worsening of atherosclerosis and increased risk of cardiovascular events.

Recent research on the KYN catabolic pathway has suggested that targeting specific enzymes within this pathway could contribute to the development of therapeutic approaches based on a mechanistic understanding. These strategies seek to regulate the balance between neuroprotective and neurotoxic metabolites by increasing levels of KYNA while decreasing concentrations of excitotoxic substances such as QA [27]. By preventing the buildup of neurotoxic substances, pharmacological or genetic intervention can pave the way for novel preventive strategies against conditions characterized by inflammation and degeneration of nerve cells [28]. By understanding how metabolites in the kynurenine pathway influence inflammatory pathways, healthcare professionals will be better equipped to develop targeted therapies that take into consideration both the underlying mechanisms and the clinical manifestations of acute cerebrovascular conditions [29].

IDO1 and KYN may also be potential therapeutic targets for hypertension in patients with systemic inflammatory conditions. Additionally, IDO1 plays an important role in the formation of atherosclerotic plaque and inflammation. By modulating IDO1, it is possible to effectively slow down the progression of atherosclerosis and reduce overall inflammation in the body [2].

Therapeutic Approaches

1. Kynurenine Metabolism Modulators

KAT activators: These agents aim to enhance the activity of KAT, promoting the conversion of KYN into KYNA. This process has neuroprotective effects, potentially reducing neurotoxicity caused by elevated levels of quinolinate, a known neurotoxic metabolite. However, the specificity of these activators and potential off-target effects should be carefully considered. Additionally, it is important to maintain a balanced ratio between neuroprotective and neurotoxic metabolites.

2. Inhibition of IDO

IDO inhibitors: IDO is the first enzyme in the kynurenine pathway, and is often increased in inflammatory conditions. By inhibiting IDO, the production of KYN and its neurotoxic metabolites can be reduced. Although reducing KYN can alleviate some neurotoxic effects, it may also impair the production of neuroprotective substances. Additionally, systemic inhibition of IDO may cause immune dysfunction.

3. TRP Precursor Supplementation

TRP supplementation: Providing TRP or its precursor may enhance serotonin synthesis and support neuroprotective effects. The efficacy of this approach may be influenced by diet and individual metabolic factors. Additionally, excessive TRP intake could lead **to elevated KYN levels and potentially exacerbate neurotoxicity.**

4. Use of Neuroprotective Agents

The direct administration of KYNA has been investigated due to its potential neuroprotective properties. While the pharmacokinetics and optimal dosing regimens for KYNA have not been fully established, further research is needed to determine these factors. Additionally, the long-term safety profile of this treatment requires further investigation to ensure appropriate monitoring and management of potential side effects.

5. Lifestyle Modifications

Diets that are rich in omega-3 fatty acids and antioxidant-rich foods may help to modulate the tryptophan-kynurenine pathway by reducing inflammation and oxidative stress. However, the impact of dietary modifications on this pathway is complex and can vary among individuals. Further research is needed to determine specific dietary recommendations based on individual needs.

Conclusions

Therefore, the kynurenine pathway represents a crucial component in the pathogenesis of acute cerebrovascular disorders, serving as a link between various pathogenic mechanisms, including systemic inflammation, excitotoxicity induced by glutamate, neuroinflammation, and oxidative stress. Future investigations in this field may lead to the development of strategies for modulating the kynurenine pathway, potentially improving treatment outcomes for ischemic stroke and other neurodegenerative conditions.

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Observational Study: Examining the Meteorological Relationship Between Subarachnoid hemorrhage

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Abstract

Background: Subarachnoid hemorrhage (SAH) is a critical condition involving bleeding into the subarachnoid space, commonly presenting with severe headache, nausea, vomiting, dizziness, and loss of consciousness. It is a significant cause of morbidity and mortality, especially in middle-aged and elderly populations, with many deaths occurring within the first 24 hours of hemorrhage onset. Some studies suggest a potential link between SAH and weather conditions, but findings are inconclusive.

Aims: This study aims to investigate the relationship between climatic conditions and SAH incidence by focusing on variables such as air temperature, dew point, humidity, weather conditions, wind speed and atmospheric pressure. Thus, patients should be aware of weather changes and take necessary precautions to reduce SAH risk factors.

Methods: A retrospective study was conducted on patients diagnosed with non-traumatic SAH admitted to a tertiary care hospital's emergency department between January 1, 2023, and December 31, 2023. Inclusion criteria were definitive diagnosis of SAH in patients aged 18 and older and subsequent hospitalization. Weather data at the time of SAH diagnosis were retrospectively reviewed, including daily average air temperature, dew point, humidity, weather conditions(fair, cloudy, windy, or rainy), wind speed, atmospheric pressure, and precipitation. Data were analyzed using SPSS 25.0, employing Pearson chi-square and Fisher's exact test for group comparisons.

Results: The study included 309 SAH patients. Significant findings include a lower average dew point and higher wind speed and atmospheric pressure on days with non-traumatic SAH admissions. SAH incidence was higher on fair and cloudy days. The lowest SAH prevalence was in June, while the highest was in January. Seasonal analysis showed the highest prevalence in spring and the lowest in autumn.

Conclusion: SAH incidence varies by month and season, decreasing in June and autumn. Climatic conditions, particularly dew point, wind speed, and atmospheric pressure, are associated with SAH occurrence. Further research is needed to fully understand the impact of weather on SAH risk.

Keywords: Subarachnoid hemorrhage; weather ; month; season.

Introduction

Subarachnoid hemorrhage (SAH) is a condition where blood enters the subarachnoid space between the pia and arachnoid membranes, and it can occur due to traumatic or spontaneous causes [1]. It is an emergency medical condition typically presenting with sudden severe headache, nausea, vomiting, dizziness, and loss of consciousness [2]. SAH is a significant cause of morbidity and mortality, especially in middle-aged and elderly populations, with a substantial proportion of deaths occurring within the first 24 hours of the hemorrhage [3].

Some studies suggest a potential link between subarachnoid hemorrhages and weather conditions

[4]. Research has both supported and refuted the impact of weather and air pollution on the occurrence of aneurysmal subarachnoid hemorrhage (SAH) [5, 6]. While some studies indicate a lower incidence of SAH in summer months, additional research has found no seasonal variation in SAH occurrence [7]. High atmospheric pressure changes are particularly noted for potentially increasing the risk of SAH, possibly due to sudden and significant changes in air pressure causing blood vessel dilation and constriction, leading to changes in blood pressure within brain arteries and thus increasing SAH risk [8]. Although studies have examined the relationship between temperature, atmospheric pressure, and other weather conditions and SAH, comprehensive and conclusive research on this topic remains lacking [9, 10]. Therefore, further investigation into the relationship between subarachnoid hemorrhage and weather conditions is warranted. Patients should be aware of weather changes and take necessary precautions to reduce risk factors [11]. This study aims to examine the relationship between climatic conditions and SAH.

Materials and methods

our retrospective study includes patients diagnosed with SAH who were admitted to the emergency department of a tertiary care hospital and subsequently hospitalized in the neurosurgery department between January 1, 2023, and December 31, 2023. Inclusion criteria were definitive diagnosis of SAH in patients aged 18 and older and subsequent hospitalization. SAH patients are non-traumatic. Patients transferred to other hospitals or with incomplete data were excluded. Demographic data of the patients were recorded, and definitive SAH diagnoses were analyzed based on patient history and computed tomography scans from the hospital's electronic records. The date of admission, season, month of admission, and weather conditions were analyzed for each patient. Weather data at the time of SAH diagnosis were retrospectively reviewed, including daily average air temperature, dew point, humidity, weather condition (fair, cloudy, windy, or rainy), wind speed, pressure, and precipitation obtained via an API storing previous weather data. Patient findings were compared with seasonal and climatic conditions.

Statistical Analysis

The database in which meteorological data and case numbers were processed was analyzed with the statistical software package SPSS version 27 (IBM Co., USA), and graphics were generated with Graphpad Prism 9. Categorical data were defined as percentages and frequencies and analyzed with a chi-square test. Numerical data were determined to be normally distributed after a distribution analysis and are presented as means ± SD. The relationship between the two sets of data was analyzed with a t-test. Among the data sets, those with p values below 0.05 were considered significant.

Results

A total of 81 patients presented to the emergency department in 2023, yielding a prevalence of 0.021%. The mean relative humidity for the 289 days without a case was found to be 55.36 ± 22.11%, while the mean relative humidity for the 76 days with a case was 49.96 ± 1.94%. No significant correlation was observed between the relative humidity and the number of cases (p = 0.053). Table 1 illustrates the correlation between meteorological variables and the incidence of cases. No statistically significant relationship was identified between weather conditions and the number of cases (p=0.303) (Table 2).

Table 1 Effect of seasonal characteristics on the number of cases

Characteristics	Free (n=289)	Case (n=76)	p-Value
Temperature (Mean±SD)	22.27±8.11	21.75±7.39	0.169
Dew Point (Mean±SD)	11.43±7.35	9.88±7.85	0.496
Humidity (%)(Mean±SD)	55.36±22.11	49.96±17.94	0.053
Wind Speed (km/H) (Mean±SD)	13.5±7.4	13.46±9.82	0.010
Pressure (Mean±SD)	1007.08±6.06	1008.07±5.57	0.366

Table 2 The impact of weather conditions on the number of cases

Conditions	Free (n=289)	Case (n=76)	p-Value
Fair	143 (%49.5)	40 (%52.6)	0.303
Windy	9 (%3,1)	5 (%6.6)	
Rainy	21 (%7.3)	1 (%1.3)	
Cloudy	116 (%40.1)	30 (%39.5)	

A comparison of the number of cases according to the seasons revealed that 15.8% of cases occurred during the autumn season, which was significantly lower than the other seasons (p=0.036). Figure 1 illustrates the number of cases according to the seasons. In the comparison of cases by month, 15.8% of cases were identified in November, while no cases were observed in July. A significant difference was observed in the distribution of cases by month (p=0.014). Figure 2 illustrates the distribution of cases by month.

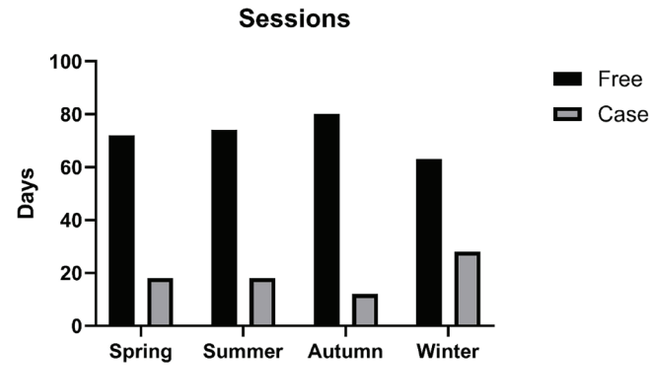

Figure 1 – Seasonal distribution of subarachnoid hemorrhages

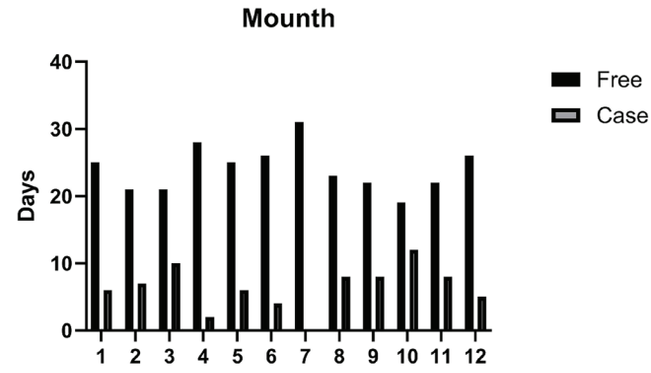

Figure 2 – Distribution of subarachnoid hemorrhages by months

Discussion

In our study, we examined the relationship between SAH incidence and seasonal, monthly, and climatic conditions such as air temperature, dew point, humidity, weather condition, wind speed, pressure, and precipitation. Our results indicate that SAH prevalence decreases in June and autumn. We found a relationship between SAH and climatic conditions such as wind speed, and higher SAH rates on fair and cloudy days.

Previous studies investigating the relationship between weather conditions and SAH have not definitively established the role of meteorological factors in SAH risk. Kockler et al. found no significant relationship between 24-hour weather changes or the absolute values of ambient temperature and relative humidity with SAH risk, reporting an uncertain SAH risk three days after exposure to high atmospheric pressure [12]. A recent multicenter study found no conclusive evidence linking weather conditions to SAH risk, suggesting adaptive mechanisms may play a role despite the lack of physiological explanations [13]. Vasquez et al. reported a potential significant relationship between ambient temperature, humidity, and SAH risk due to the sensitivity of cerebral perfusion to PaCO2 variability [14]. Another study suggested that changes in atmospheric gases leading to hypocapnia could contribute to SAH incidence, with high and low temperature combinations being associated with SAH occurrence [15]. Gill et al. found that a one-day drop in temperature and colder daily temperatures were linked to an increased risk of aSAH cases, independent of season, particularly during autumn when transitions from warm to cold occur [8]. A detailed review found an association between spontaneous SAH and temperature and humidity [16]. Lai et al. reported that increased sunshine and higher average morning humidity were associated with reduced hospital admissions due to ruptured cerebral aneurysms [16]. Our findings align with these studies, showing a relationship between SAH and wind speedwith higher SAH rates on fair and cloudy days.

Seasonal and monthly variations in SAH incidence have also been noted, with increased SAH admissions in winter and January linked to reduced sunlight [16]. Peters et al. found that SAH occurrence varied with seasons, being less frequent in summer and most common in January [17]. McDonald et al. showed that SAH was unrelated to temperature but was linked to climate, independent of mortality [18]. Huang et al. identified peak SAH onset periods in March (spring) and December (winter), with cold and extreme atmospheric pressure as triggers [19]. Our study found similar results, with reduced SAH prevalence in June and autumn.

Limitations

Our study has some limitations. The relationship between disease factors and climate changes could not be fully determined. Additionally, it was not possible to precisely identify sudden climatic fluctuations based on weather information at the time of admission. The exact onset time of the disease and symptoms was also unknown, representing a significant limitation. Prospective and multicenter studies are needed to understand the value of our findings.

Conclusıons

SAH admissions vary by month and season, with decreased prevalence in June and autumn. We found a relationship between SAH and dew point, wind speed, and pressure, with higher SAH rates on fair and cloudy days.

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Vaccination Literacy and Determinants of Vaccine Confidence Among University Students: Analyzing Attitudinal Barriers

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Abstract

Introduction: Vaccination literacy plays a critical role in shaping vaccine attitudes and acceptance, especially among university students who are exposed to diverse sources of information. In Kazakhstan, limited awareness of the HPV vaccine, with only 52% of women attending gynecological clinics being informed, underscores a significant knowledge gap that demands effective communication strategies and public education. Addressing this gap has the potential to improve vaccine uptake and advance public health outcomes. This study aims to assess the level of vaccination literacy among students in Karaganda, Kazakhstan, and examine its determinants, including gender, academic field, and residence.

Methods: Using the HLS19-VAC questionnaire, we surveyed 1,327 students across different academic fields and analyzed vaccination literacy levels. A chi-square test assessed the association between literacy and demographic variables. Vaccination literacy was categorized as inadequate, problematic, adequate, or excellent.

Results: The majority of students demonstrated “adequate” or “excellent” vaccination literacy, with medical, female, and urban students exhibiting higher literacy levels. However, significant misconceptions regarding vaccine safety and side effects persisted, even among students with higher literacy. A positive association was observed between vaccination literacy and vaccine uptake, reinforcing the influence of informed literacy on health behavior.

Conclusion: The findings highlight the need for targeted educational efforts to address misconceptions and reduce literacy gaps among different demographic groups. Public health campaigns that counter vaccine myths and promote trust are essential for improving vaccine acceptance and supporting health outcomes within the university student population.

Keywords: Vaccination literacy, vaccine acceptance, university students, public health.

Introduction

Vaccination is a cornerstone of public health, reducing infectious diseases and improving well-being. It is essential for achieving herd immunity, with COVID-19 requiring vaccination rates of 78% to 89% [1]. Routine childhood vaccination has significantly contributed to the global decline in child mortality rates from 1970 to 2016, as reported by the Global Burden of Disease Study, highlighting the impact of increased vaccination coverage [2]. Vaccine hesitancy and misinformation, amplified by the COVID-19 pandemic and social media, have hindered immunization efforts, particularly among students, by reducing vaccine acceptance [3, 4]. Despite 98% of medical students acknowledging the importance of COVID-19 vaccines, 23% hesitated to receive it immediately after approval, primarily due to misinformation, perceived risks, and distrust in health authorities [5–7]. Targeted interventions improving vaccination literacy and involving trusted medical professionals can reduce misinformation and foster positive vaccine attitudes among students [7, 8]. Additionally, understanding the specific concerns and barriers faced by students can inform the development of effective strategies to

enhance vaccine acceptance [6, 9].

The relationship between health literacy and vaccination uptake is well-documented, indicating that individuals with higher health literacy are more likely to understand the importance of vaccines and, consequently, participate in vaccination programs [10; 11]. In Kazakhstan, where vaccine hesitancy has been a significant barrier to achieving herd immunity, enhancing health literacy is vital for improving vaccination rates. Lorini et al. has shown that health literacy encompasses not only the ability to read and understand health-related information but also the capacity to apply this knowledge effectively in making health decisions [11].

Aimagambetova et al. highlight the critical role of communication strategies and public education in addressing low awareness and negative perceptions of the HPV vaccine among women in Kazakhstan [12]. Issa et al. reveals that only 52% of women attending gynecological clinics were familiar with the HPV vaccine, underscoring a substantial knowledge gap requiring urgent intervention [13].

Vaccination literacy (VL) is essential for informed vaccine decisions, encompassing awareness, understanding of vaccine safety and efficacy, and the ability to critically evaluate information credibility [14; 15]. Higher vaccination literacy increases vaccine acceptance and advocacy, as evidenced by university students with better literacy showing greater willingness to receive the COVID-19 vaccine [16].

Enhancing vaccination literacy among students can reduce hesitancy and misinformation, enabling informed health decisions through educational interventions [17, 18]. University students' vulnerability to social media misinformation highlights the need to enhance vaccination literacy. In line with it, the study aims to assess the level of vaccination literacy among students in the city of Karaganda and examine the factors influencing vaccination literacy.

Materials and Methods

Participants were recruited based on the following inclusion criteria as enrollment as a student in Medical, Humanities Sciences, or Technical programs at higher educational institutions. Invitations to participate were disseminated to universities in Karaganda offering undergraduate programs in the specified fields. The invitations provided detailed information about the study objectives, the health literacy (HL) assessment tool, and the potential benefits of participation.

Three universities consented to participate and granted the research team access to their student populations. Designated university staff responsible for student engagement facilitated meetings between the research team and students. These sessions included a comprehensive briefing on the study objectives and detailed instructions for completing the questionnaire. Participants were given the option to complete the questionnaire either in paper format or electronically through a QR code linked to a Google Forms survey. Informed consent was obtained from all participants prior to their inclusion in the study.

The HLS19-VAC questionnaire is a four-item survey designed to measure adult population literacy in the field of vaccination and is part of the HLS19 health literacy measurement tools (HL) group [19]. The Local Bioethics Commission of the Medical University of Karaganda approved the study on 11 October 2022 (Protocol 1), with participants giving informed consent, receiving questionnaire instructions, and participating voluntarily with the option to withdraw at any time. The HLS19-VAC instrument has been applied in large samples across multiple countries, demonstrating its reliability and validity in diverse settings. The instrument's psychometric properties have been evaluated, confirming its suitability for assessing vaccination literacy in general adult populations [19].

Each survey question was rated on a four-point Likert scale, ranging from "very easy" to "very difficult," depending on the perceived level of difficulty. As such, the HLS19-VAC questionnaire represents a "subjective" version based on respondents' perceptions.

Vaccination literacy, as a significant indicator, can only be assessed for respondents with a complete data set for the four vaccination literacy items:

$$VL = \frac{(\text{Number of "easy" or "very easy" responses})}{4} * 100 \text{ [26].}$$

The result for vaccination literacy is expressed as a percentage and can take values of 0, 25, 50, 75, or 100. The classification thresholds for vaccination literacy are based on the following criteria: below 66.66 ("inadequate") and above 66.67 ("adequate").

To compare the distribution of categorical variables across groups, a chi-square test was conducted. This test assessed the relationship between variables and different groups. A p-value below 0.05 indicated a statistically significant difference.

Results

The survey involved 1327 students from 1st to 5th year. The largest proportion of respondents were 1st-year students (50.19%), while 2nd and 3rd-year students each accounted for 17.49%. The 4th-year students made up 12.06% of the total, and the smallest proportion of respondents were 5th-year students, at 2.71%.

The survey was conducted across three academic fields. The distribution of respondents by field was as follows: 27.16% in the humanities, 46.05% in medical fields, and 26.76% in technical fields.

The average vaccination literacy among students was 82.61 ± 29.25. A total of 265 students had "inadequate" vaccination literacy, while the majority, 1062 individuals, demonstrated an "adequate" level of vaccination literacy.

The levels of vaccination literacy within the sample are presented as follows: the "adequate" level is observed in 52% of females and 28% of males; the "inadequate" level is seen in 12.2% of females and 7.8% of males (Table 1). However, the chi-square analysis ($\chi^2 = 1.360$, $p = 0.243$) found no statistically significant relationship between gender and VL.

Table 1 Demographic Characteristics and Vaccination Literacy

Indicators/Vaccination Literacy Levels		Inadequate		Adequate		Chi-square; p-value
		n	%	n	%	
Gender	female	162	12,2	690	52,0	1,360; 0,243
	male	103	7,8	372	28,0	
Year of Study	1	111	8,4	555	41,8	22,360; 0,0001
	2	63	4,7	169	12,7	
	3	58	4,4	174	13,1	
	4	32	2,4	128	9,6	
	5	1	0,1	35	2,6	
Place of Residence	Rural area	108	8,1	397	29,9	5,123; 0,077
	Urban area	156	11,8	665	50,1	
Education Program	Humanities	92	6,9	269	20,3	22,227; 0,0001
	Medical	88	6,6	523	39,4	
	Technical	85	6,4	270	20,3	

In terms of field of study, medical students had the highest percentage of "adequate" VL (39.4%), followed by students in technical fields (20.3%) and humanities (20.3%). A chi-square analysis confirmed a statistically significant association between VL levels and academic discipline ($\chi^2 = 22.227$, $p < 0.0001$).

Place of residence also influenced VL, with 50.1% of urban students achieving “adequate” VL, compared to 29.9% of rural students. Inadequate literacy was slightly higher among urban (11.8%) than rural students (8.1%). However, chi-square test didn’t show a significant relationship between residence and VL levels ($\chi^2 = 5.123$, $p = 0.077$).

The majority of the participants, 90.7% reported receiving a vaccine within the past five years, with 73.9% demonstrating "adequate" VL and 16.8% showing "inadequate" VL, confirming a statistically significant association between VL and vaccination rates ($\chi^2 = 36.619$, $p < 0.0001$).

Participants' opinions on the effects of vaccines on the immune system also varied based on their VL. While 57.6% disagreed with the belief that vaccines weaken the immune system, 41.8% agreed. Among those with "adequate" VL, 49.3% disagreed with this statement, compared to 30.4% who agreed (Table 2). The association between VL and these opinions was found to be significant ($\chi^2 = 36.619$, $p < 0.0001$). Similarly, 39.5% of participants believed that vaccines could cause the diseases they are designed to prevent, while 59.8% disagreed. Among respondents with "adequate" VL, 29.6% agreed with this misconception, and 50.1% disagreed, showing a significant association between VL and beliefs about vaccine-caused disease ($\chi^2 = 20.191$, $p < 0.0001$). Concerns about severe side effects were expressed by 51.1% of participants, with 38.1% of those with "adequate" VL agreeing and 41.4% disagreeing. A statistically significant link between VL and opinions on vaccine side effects was confirmed ($\chi^2 = 32.066$, $p < 0.0001$).

Table 2 Vaccination Literacy Levels and Survey on the Effects of Vaccines on the Immune System

Questions		Inadequate		Adequate		Chi-square; p-value
		n	%	n	%	
Have you or your family members received any vaccines in the past five years?	Yes	223	16,8	981	73,9	17,518; 0,0001
	No	37	2,8	74	5,6	
Vaccines overload or weaken the immune system	Agree	151	11,4	403	30,4	36,619; 0,0001
	Disagree	110	8,3	654	49,3	
Vaccines may cause the diseases they are supposed to protect against	Agree	132	9,9	393	29,6	20,191; 0,0001
	Disagree	129	9,7	665	50,1	
Vaccines often cause severe side effects (excluding typical, temporary reactions in the first few days)	Agree	172	13,0	506	38,1	32,066; 0,0001
	Disagree	88	6,6	550	41,4	
Vaccination is important to protect myself and my children	Agree	156	11,8	925	69,7	117,794; 0,0001
	Disagree	104	7,8	136	10,2	
Overall, I consider vaccination to be safe	Agree	135	10,2	854	64,4	102,511; 0,0001
	Disagree	126	9,5	207	15,6	
Overall, I consider vaccination to be effective	Agree	141	10,6	876	66,0	106,631; 0,0001
	Disagree	120	9,0	185	13,9	
Vaccination aligns with my religious beliefs	Agree	144	10,9	825	62,2	64,991; 0,0001
	Disagree	116	8,7	235	17,7	
Vaccination is important to prevent the spread of serious diseases	Agree	168	12,7	957	72,1	125,970; 0,0001
	Disagree	92	6,9	105	7,9	
How high do you consider the risk of developing vaccine-preventable diseases if not vaccinated?	Low	110	8,3	295	22,2	25,292; 0,0001
	High	148	11,2	757	57,0	

The majority of participants (81.5%) valued vaccination as essential for personal and family protection, with 69.7% of those with "adequate" VL supporting this view. The chi-square analysis confirmed that VL significantly influenced opinions on the importance of vaccination ($\chi^2 = 117.794$, $p < 0.0001$). Regarding vaccine safety, 74.6% of participants considered vaccines safe, with 64.4% of respondents with "adequate" VL agreeing with this statement ($\chi^2 = 102.511$, $p < 0.0001$). Furthermore, 76.6% rated vaccination as effective, with 66% of participants with "adequate" VL strongly agreeing ($\chi^2 = 106.631$, $p < 0.0001$).

In addition, VL was significantly associated with beliefs about the compatibility of vaccination with religious views, as 62.2% of those with "adequate" VL agreed that vaccination aligns with their religious beliefs ($\chi^2 = 64.991$, $p < 0.0001$). Participants' perception of the risk of vaccine-preventable diseases also varied by VL. Among those with "adequate" VL, 57% rated the risk as high if not vaccinated, highlighting a significant association between VL and risk perception ($\chi^2 = 25.292$, $p < 0.0001$).

Discussion

This study provides valuable insights into vaccination literacy among university students, highlighting both promising trends and critical areas for improvement. A significant finding is that the majority of students exhibited "adequate" vaccination literacy, reflecting a generally well-informed population capable of making informed health decisions. Such literacy is crucial for promoting vaccine uptake, countering misinformation, and supporting public health efforts [20, 21].

However, disparities in vaccination literacy were evident across different subgroups. Significant variations were observed based on the year of study, field of study, and geographic location. Interestingly, no significant differences in health literacy levels were found between genders. While prior studies suggest that gender-specific educational strategies can improve engagement and comprehension, these findings indicate that broader, inclusive approaches may also be effective [22, 23].

Unsurprisingly, medical students demonstrated the highest vaccination literacy levels, likely due to their academic exposure to health-related information. This supports the notion that

educational background and field of study are closely linked to health literacy [24; 25]. Furthermore, students from urban areas outperformed their rural counterparts, highlighting geographic disparities in access to health education. The lower literacy levels among rural students underscore the need for targeted, region-specific programs that address barriers to information access unique to these communities [26, 27].

The positive association between vaccination literacy and vaccine uptake further underscores the importance of fostering health literacy. Students with higher literacy levels were more likely to be vaccinated, demonstrating that well-informed individuals are better equipped to evaluate health information, overcome vaccine hesitancy, and make confident vaccination decisions [28, 29]. Moreover, these students displayed greater confidence in vaccine safety, efficacy, and compatibility with personal and religious beliefs, highlighting the role of health literacy in shaping positive vaccination attitudes.

Despite these encouraging trends, significant misconceptions persist, with fewer than half of the students believed vaccines could not cause the diseases they aim to prevent, and concerns about severe side effects were prevalent among more than half of the participants. These misconceptions indicate persistent gaps in understanding, which demand targeted educational interventions. Research has consistently shown that misinformation, particularly around vaccine safety, is a major barrier to vaccine acceptance [30]. For instance, Shengelia (2021) warns that misinformation and "fake news" undermine public trust in vaccines, fueling hesitancy [31]. Similarly, Bogart et al. (2021) emphasize that mistrust is especially pervasive in marginalized communities, where misinformation exacerbates resistance to vaccination [32].

Improving vaccination health literacy among students is critical for reducing vaccine hesitancy and supporting public health. Tailored educational programs, as emphasized by Shon and Lee, effectively enhance knowledge and vaccine confidence by addressing students' specific health beliefs and literacy levels [14]. Integrating health literacy into school curricula further supports this goal, fostering informed decision-making and reducing health inequities [33]. Additionally, leveraging technology and social media offers scalable ways to engage students, build trust, and counter misinformation [34]. Combining these strategies ensures a comprehensive approach to improving vaccination literacy and promoting vaccine acceptance, ultimately advancing public health outcomes.

This study has certain limitations that should be acknowledged. First, the reliance on self-reported data to evaluate vaccination literacy may have introduced biases, as participants might overestimate or underestimate their actual knowledge. Second, the cross-sectional design of the study only provides a snapshot of the data, which restricts the ability to draw causal inferences or track changes over time. Despite these limitations, the study's notable strength lies in the application of validated instrument, which enhances the reliability and validity of the findings and adds robustness to the overall data quality.

Conclusion

This study provides an in-depth analysis of vaccination literacy among university students, revealing both strengths and challenges in promoting informed health decisions. A majority of students demonstrate "adequate" vaccination literacy, indicating a promising ability to make informed choices and resist vaccine misinformation. These findings highlight the need for targeted educational strategies to bridge literacy gaps and enhance access to reliable vaccination information. Additionally, persistent misconceptions about vaccine safety and side effects signal an ongoing need for public health campaigns that effectively address common myths and emphasize the scientific rigor behind vaccine safety. Enhancing vaccination literacy and addressing demographic disparities can promote positive health behaviors and support public health goals within university communities, ultimately contributing to improved health outcomes.

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COVID-19 Coronavirus Infection and Trimesters: Is There a Link?

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Abstract

Objectives: Despite serious challenges, humanity has been able to adapt and take measures to limit the spread of COVID-19 and minimize its negative consequences. This pandemic has emphasized the importance of global collaboration, scientific and medical progress, and raised questions about the need to strengthen health systems and international crisis response mechanisms. Although humanity continues to face new challenges associated with COVID-19, including the emergence of new strains, the development and introduction of vaccines and effective therapeutic agents have raised hope for overcoming the pandemic and creating a more sustainable health system for the future. The aim of our study was to investigate the course of the disease according to trimesters.

Material and methods: We retrospectively analyzed the case histories of women with COVID-19 coronavirus infection treated in the mentioned hospitals between December 2020 and February 2022. The study considered the following parameters according to the trimester of pregnancy: number of previous pregnancies, age, disease severity and presence of comorbidities.

Results: Mild COVID-19 accounted for a smaller proportion of the sample (3.2-13%) due to treatment at home or in outpatient settings. More than half of those hospitalized (209 – 51.0%) were admitted in severe condition. Analysis of COVID-19 severity distribution by trimester showed statistically significant differences ($p<0.05$). Associated diseases were detected in 306 patients, accounting for 74.6% of all cases. Statistically significant differences were found when evaluating comorbidities according to trimester. The main complaints included dry cough (394), weakness (388), sore throat (372), fever (367), malaise (365) and headache (287).

Conclusions: Infection is more frequently observed in pregnant women in the third trimester, which may be related to the increased frequency of diagnosis in this period. The presence of comorbidities is a factor that increases the severity of the condition.

Keywords: COVID-19, pregnancy, symptoms, trimesters, SARS-Cov-2

Introduction

The 21st century began with a thorough rethinking of the epidemic and pandemic potential of betacoronaviruses, which required a control system as multilayered as that for influenza. This system covers all stages – from the natural reservoir of the virus, which is bats (Chiroptera, Microchiroptera), to the organization of prophylactic and anti-epidemic measures. [1].

COVID-19 is characterized by a lower maternal mortality rate than SARS or Middle East respiratory syndrome. Asymptomatic women may develop respiratory symptoms after delivery. [2]. Therefore, it is important for physicians of all specialties to consider the possibility of asymptomatic forms of the disease, as they most often remain undetected and unrecognized. In a study by Abuova G. et al. it was found that ultrasonography revealed oligohydramnios in 85% of cases, premature aging of the placenta and placental cysts in 27.5%, and impaired blood flow in utero-fetal-placental circulation in 12.5% of cases. [3]. Subsequently, more than half (51.4%) of the women gave birth at term. However, 48.5% of patients had preterm labor.

Pregnant women with COVID-19 infection are known to be at high risk not only because of an increased likelihood of severe infection and pneumonia, but also because of an increased incidence of placental-associated pregnancy complications [4].

Placental-associated complications of pregnancy are categorized as major obstetric syndromes that include conditions such as preeclampsia, preterm labor, and fetal growth retardation. [5]. To date, there are publications indicating that pregnant women with pneumonia are more likely than other groups to experience preterm labor and low birth weight preterm infants [6, 7].

Despite serious challenges, humanity has been able to adapt and develop measures to limit the spread of COVID-19 and prevent its negative consequences [8]. The pandemic emphasized the importance of global cooperation, scientific and medical progress, and emphasized the need to strengthen health systems and international crisis response mechanisms.

Humanity continues to face new COVID-19 challenges, including the emergence of new strains [9]. However, the development and introduction of vaccines and effective treatment methods have raised hope for overcoming the pandemic and creating a more sustainable health care system in the future. Our study was aimed at investigating the peculiarities of the course of the disease depending on the trimester of pregnancy.

Material and methods

The study was conducted on the basis of the city infectious disease hospital, infectious disease center and perinatal center of Shymkent city. It was a cohort, non-interventional clinical study.

The work was approved by the Ethical Committee of JSC "South Kazakhstan Medical Academy" on November 21, 2020 in accordance with the protocols of the Helsinki Declaration of 1964. The conclusion of the ethical committee is recorded in protocol #1 dated March 16, 2021. All study participants gave consent to participate after signing informed consent. The study was based on the protocols "Coronavirus infection in pregnant women, women in labor and delivery" and "Coronavirus infection in adults".

We retrospectively analyzed the medical histories of women with COVID-19 treated at the mentioned institutions between December 2020 and February 2022. The study examined parameters such as the number of previous pregnancies, age groups, disease severity, and the presence of comorbidities depending on the trimester of pregnancy.

Statistics. The normality of the distribution was checked according to Kolmogorov-Smirnov with the Lilliefors correction. Since all data showed a normal distribution, the mean and standard deviation were subsequently used. Categorical variables are presented as absolute numbers, percentages, and frequencies. A $p<0.05$ value was considered statistically significant. Statistical processing of the obtained data was carried out using the IBM SPSS Statistics 26.0 program.

Ethics

The study was approved by the Local Bioethical Committee of JSC "SKMA" (date: 03/16/2021). Written informed consent for publication in the article was obtained from patients or their legal representatives.

Results

Comparison of pregnancy parity according to trimester revealed, in the first trimester the median rate was 3.00 (Q -Q13 : 1-5), in the second trimester it was 3.00 (Q -Q13 : 2-4) and in the third trimester it was 3.00 (Q -Q13 : 2-5) (Table 1).

The patients were divided into age groups as shown in Figure 1: 18-20 years, 21-25 years, 26-30 years, 31-35 years, 36-40 years and 41-50 years. The largest number were women aged 26 to 35 years – 223 (54.4%). The smallest group consisted of pregnant women aged 41-50 years with only 10 (2.4%). The younger age group of 18-20 years was found in 21 cases (5.1%). The sample included all age groups, including both women of early and late reproductive age.

Table 2 shows the predominance of the age group between 26 and 30 years during the first two trimesters of pregnancy where this age range was 36.0% and 28.7% respectively. In the third trimester, pregnant women between 31 and 35 years of age accounted for 30.7%.

Table 1 Distribution of indicators by trimester of pregnancy

Indicator		Trimesters of pregnancy			p
		1 trimester n=50	2 trimester n=122	3 trimester n=238	
Pregnancy Parity Me (Q -Q)13		3 (1-5) Min=1 Max= 8	3 (2-4) Min=1 Max= 8	3 (2-5) Min=1 Max=9	0,685
Ages groups, abs.%	18-20 years old	4 (8,0)	7 (5,7)	10 (4,2)	0,565
	21-25 years old	14 (28,0)	31 (25,4)	48 (20,2)	
	26-30 years old	18 (36,0)	35 (28,7)	61(25,6)	
	31-35 years old	7 (14,0)	29 (23,8)	73 (30,7)	
	36-40 years old	6 (12,0)	18 (14,8)	39 (16,4)	
	41-50 years old	1 (2,0)	2 (1,6)	7 (2,9)	
Severity abs.%	Light	1 (2,0)	5 (4,1)	7(2,9)	0,000 *
	Average	32(64,0)	64(52,5)	51(41,8)	
	Heavy	7(2,9)	69(29,0)	141(59,2)	
	Extremely difficult	0	2(1,6)	21 (8,8)	
Presence of comorbidities abs.%	Yes	27 (8,8)	82 (26,8)	196 (64,4)	0,005 *
	No	23 (21,9)	40 (38,1)	42 (40)	
Number of bed days,abs.%	1-7 days	27 (13,8)	59 (30,1)	110 (56,1)	0,208
	8-15 days	18 (9,9)	49 (27,1)	114(63,0)	
	16 or more	5(15,2)	14(42,4)	14(42,4)	

** Differences of indicators are statistically significant (p<0.05)*

Table 2 Number of bed days spent by age groups of pregnant women with COVID-19

Number of bed days, abs.%	Age groups						P
	18-20 years old	21-25 years old	26-30 years old	31-35 years old	36-40 years old	41-50 years old	
1-7 days	9(4,6)	43(21,9)	55(28,1)	56(28,6)	29(14,8)	4(2,0)	p=0,04* p=0,007*
8-15 days	12(6,6)	46(25,4)	53(29,3)	43(23,8)	24(13,3)	3(1,7)	
16 or more	0	4(12,1)	6(18,2)	10(30,3)	10(30,3)	3(9,1)	

** Differences of indicators are statistically significant (p<0.05)*

The next indicator we investigated was the severity of COVID-19 coronavirus infection in hospitalized pregnant women. As shown in Figure 2, mild COVID-19 accounts for a smaller proportion of the sample (3.2% or 13 cases), which is due to the fact that most of the patients were treated at home or as outpatients. More than half of hospitalized women (209, or 51.0%) were in severe condition at the time of admission.

Analysis of COVID-19 severity according to trimester of pregnancy showed statistical significance (p<0.05), indicating that the severity of the disease increased with increasing gestational age and progression to later trimesters.

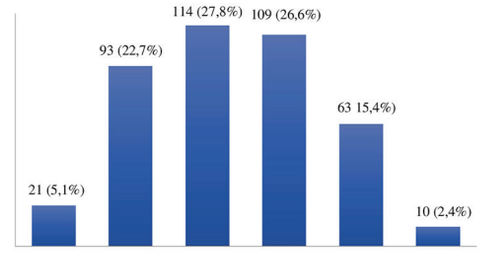

Figure 1 – Age groups of pregnant women with COVID-19 coronavirus infection

Table 3 Disease severity according to age groups in the studied subjects

Disease severity, abs.%	Age groups						P
	18-20 years old	21-25 years old	26-30 years old	31-35 years old	36-40 years old	41-50 years old	
Light	0	3(3,2)	4(3,5)	3(2,8)	2(3,2)	1(10,0)	p=0,04 *
Medium	14(66 ,7)	53(57, 0)	53(46, 5)	27(4,8)	15(23 ,8)	3(30,0)	p=0,02 *
Heavy	7(33, 3)	36(38, 7)	53(46, 5)	72(66,1)	38(60 ,3)	3(30,0)	
Extremely heavy	0	1(1,1)	4(3,5)	7(6,4)	8(12, 7)	3(30,0)	

** Differences of indicators are statistically significant (p<0.05)*

Comorbidities were identified in 306 patients, accounting for 74.6% of the total number of patients studied. We found statistically significant differences in the presence of comorbidities depending on the trimester of pregnancy. Among the concomitant diseases, diseases of the circulatory system prevailed (50%), which is associated with a physiological decrease in hemoglobin during pregnancy. 21% of women had respiratory diseases, 13% – diseases of the circulatory and urinary system, 3% – diseases of the endocrine system.

For convenience in analyzing the length of hospital stay, bed days were divided into three categories:1-7 days;8-15 days;16 or more days.

Table 2 shows that 196 pregnant women (47.8%) were medically treated in infectious diseases hospitals for 1-7 days. Of these, 27 (13.8%) were in the first trimester, 59 (30.1%) were in the second trimester, and 110 (56.1%) were in the third trimester. 181 patients (44.1%) spent 8 to 15 days in a health care facility with a diagnosis of COVID-19. Among them, 18 (9.9%) were between 1 and 12 weeks' gestation, 49 (27.1%) between 13 and 28 weeks' gestation, and 114 (63.0%) between 29 and 40 weeks' gestation. 33 pregnant women (8.1%) spent 16 or more days in hospital: 5 (15.2%) of them were in the first trimester, 14 (42.4%) in the second trimester and 14 (42.4%) in the third trimester. We analyzed nominal scales using Pearson's chi-square test. When comparing age groups according to the number of bed days, statistically significant differences were obtained (p=0.04). These differences were due to the absence of cases with 16 or more bed days in the 18-20 age group (p=0.007). A moderate association was recorded between the compared features (V=0.216).

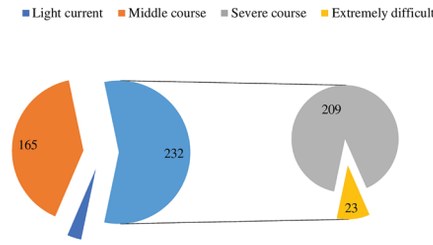

Figure 2 – COVID-19 severity in hospitalized pregnant women

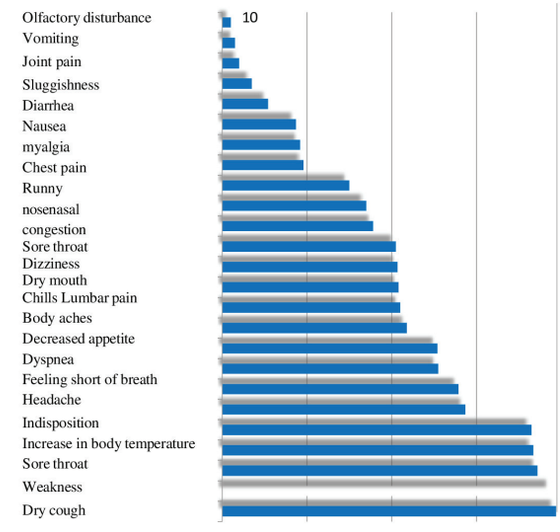

Figure 3 – Complaints at the time of examination in pregnant women with COVID-19

45% (9) of pregnant women in the age group of 16 to 20 years were admitted to hospital within the first three days after the onset of symptoms. At the same time, only 3.9% (4) of women over 31 years of age sought medical care 15 days after the onset of their first complaints. Under 30 years of age, the majority of pregnant women received inpatient care within the first three days of illness, while women in the older age group (31 years and older) sought medical care later, on the 4th day of illness.

The sample included patients with different degrees of disease severity: mild – 13 cases (3.17%), moderate – 165 cases (40.24%), severe – 209 cases (50.97%) and extremely severe – 23 cases (5.6%). Distribution by age groups is presented in Table 3.

During the study, nominal scales were analyzed using Pearson's chi-square criterion. Statistically significant differences (p=0.000) were found when comparing age groups according to disease severity. These differences were due to the fact that moderate severity was more common in patients between 16 and 30 years of age, while severe severity was more prevalent in women over 31 years of age (p=0.02). There was a fairly high correlation between the compared features (V=0.516). At the same time, cases of extreme severity were not registered in pregnant women of early reproductive age (18 – 20 years).

Figure 4 illustrates the symptoms characteristic of the patients during the disease. The most common complaints were dry cough (394 cases), weakness (388 cases), sore throat (372 cases), increased body temperature (367 cases), malaise (365 cases) and headache (287 cases). The least common symptoms were impaired sense of smell (10 cases), vomiting (15 cases), joint pain (20 cases), lethargy (35 cases) and diarrhea (54 cases).

Discussion

In our study, it was found that the number of bed days spent by patients in hospital decreases with increasing age. Pairwise comparison of groups revealed that COVID-19 coronavirus infection was more commonly reported in pregnant women at 28-40 weeks' gestation, especially those with a history of comorbidities. For example, one UK study showed that most of the 427 pregnant women hospitalized with COVID-19 between March 1 and April 14, 2021 were in the late second trimester or third trimester [10, 12, 13]. In pregnant women with COVID-19, it is possible for a critical condition to develop rapidly against the background of a relatively stable course of the disease. Pregnant women experience changes in the respiratory system, including an increase in lung volume and a decrease in respiratory function due to uterine growth. These factors can make it difficult for the body to fight respiratory infections such as COVID-19. In addition, pregnant women have an increased risk of complications, including preeclampsia and premature birth, which can worsen due to coronavirus infection. As a result of these circumstances, pregnant women may face a higher risk of developing severe symptoms requiring hospitalization and intensive care [11, 19, 23, 24].

The presence of comorbidities such as cardiovascular, hepatic and renal pathologies and diabetes mellitus affects the course of COVID-19 in pregnant women [11, 14]. The time of admission to hospital to receive specialized care is of paramount importance to achieve positive treatment outcomes, which is particularly important for both mother and child [15–19].

We also investigated the body mass index (BMI) of the women. The analysis showed that 20.7% of pregnant women had a normal BMI (18.5 to 24.9), while 79.3% were overweight or obese. In our sample, obesity (BMI>30) was found in 29.3% of pregnant women. Previous studies confirm the significant impact of overweight and obesity on the increased morbidity and mortality of COVID-19 [20–22]. In another study, 19 (20.7%) out of 92 pregnant women had BMI within normal range, while 73 patients (69.3%) were overweight and 27 (39.3%) were obese, which is probably due to hypodynamia against strict quarantine measures and unbalanced diet [22]. Pregnant women who contracted COVID-19 at 1–12 weeks (13 – 26.0%) were more likely to recover compared to women at later gestation.

The presence of respiratory symptoms and the need for hospitalization increased significantly with later trimesters in pregnant women with COVID-19 [24].

Recruitment of pregnant women with COVID-19 during the pandemic has been rapid, which is one of the strengths of the study. However, the study was conducted in only one city, that was the limitation. In the future, we plan to conduct research in other cities. Another limitation was that this study is single center, which does not provide extended results. It should be noted that the sample size was relatively small.

Conclusions

Trimesters of pregnancy influence the course of the disease. The highest incidence of infection is observed in pregnant women in the third trimester, which is associated with increased diagnosis of women in this period. Associated diseases act as triggers for worsening of the patients' condition. Data analysis also showed that the severity of the disease increases with increasing gestational age or later trimesters.

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The Effect of Calcium on Premenstrual Syndrome: A Meta-Analysis Study

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Abstract

Aims. This study systematically reviewed the available randomised controlled trials to elucidate the general relationship between calcium and PMS.

Material and Methods. Meta-analysis followed PRISMA guidelines using the PICOS format, considering CONSORT recommendations. Searches were performed in PubMed, Web of Science, Google Scholar, and Scopus databases between 02.11.2022- 02.12.2022 using the keywords "premenstrual syndrome and calcium" and "premenstrual tension and calcium" and "premenstrual dysphoric disorder and calcium". The search strategy was applied to articles published between January 2012 and December 2022. The Cochrane tool was used to assess the risk of bias in RCTs. Fixed-effect models and random-effect models were used for meta-analysis based on heterogeneity. Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines were followed in our study.

Results. This systematic review and meta-analysis included six randomised controlled trials published between 2013 and 2020. According to the pooled results of the six studies, calcium reduced the severity of PMS complaints (p=0.002; I2 = 76.2%) when calcium administration was compared with the control group for the reduction of PMS complaints. On the other hand, the severity of PMS complaints did not change when calcium administration for the reduction of PMS complaints was compared with other treatments (p=0.416; I2 = 54.7%).

Conclusions. This study showed that calcium effectively reduced the severity of PMS complaints compared to the control groups. In contrast, the severity of PMS complaints did not change when other treatments and calcium administration were compared.

Keywords: PMS, calcium, randomized controlled, meta-analysis.

Introduction

Premenstrual syndrome (PMS) is a common condition that affects the health of millions of women of reproductive age worldwide [1]. PMS is characterised by clinically significant psychological and physical symptoms. PMS, which occurs during the luteal phase of the menstrual cycle, ends with the onset of menstrual bleeding [2–5]. PMS is defined as a clinical condition characterised by emotional and physical symptoms that begin on the 5th day before the menstrual period and end around the 4th day after the menstrual period, and is not associated with any physiological disease [6].

Although PMS is thought to occur as a result of hormonal changes that accompany ovulation, the cause is not known for certain [7]. The hormone progesterone plays an important role in the mechanism of PMS. Progesterone metabolites bind to the gamma-aminobutyric acid (GABA) receptor in the brain, changing the structure of the GABA receptor and reducing its sensitivity. As a result, serotonin levels decrease and PMS symptoms occur [7]. Premenstrual symptoms have a significant impact on women's quality of life, increasing healthcare utilisation and reducing work productivity [8]. Among women of reproductive age, 47.8% experience PMS symptoms [5]. Twenty per cent of these women experience

symptoms so severe that they are unable to carry out their daily work, and the remainder experience mild to moderate symptoms. The clinical symptoms of PMS can be divided into two groups: psychological and somatic. While psychological symptoms include social isolation, aggression, fatigue, suicidal thoughts, irritability and depression, somatic symptoms include oedema, weight gain/loss, stiff/low back and headaches, breast tenderness, swelling, changes in diet and oedema [2–9]. Pharmacological and non-pharmacological treatments are used to reduce PMS symptoms. Non-pharmacological treatments are used to treat mild symptoms, while pharmacological treatments, serotonin reuptake inhibitors (SSRIs), are used to treat severe symptoms [8].

Non-pharmacological treatments are called complementary therapies and are safer and have fewer complications than pharmaceutical methods [10]. Examples of these treatments include aerobic exercise, cognitive behavioural relaxation therapy, magnesium/vitamin B6/D or L-tryptophan supplementation, or complex carbohydrate intake [11]. The literature highlights the relationship between fluctuations in calcium levels and PMS symptoms. It is known that serum calcium levels are reduced prior to the menstrual period, are lower in the luteal phase of the menstrual cycle than in the follicular phase, and this low level can exacerbate PMS symptoms by causing hallucinations, depression and restlessness [12–14]. Several studies have shown that calcium may be beneficial in alleviating psychotic disorders associated with PMS. Some interventional studies have shown that calcium supplementation is associated with a reduction in the incidence of various symptoms of PMS [15,16], and there are also studies in the literature suggesting that there is no association [17, 18].

It can be seen that there are conflicting results in the literature regarding the studies that have investigated the relationship between the severity of PMS symptoms and calcium supplementation. This trial was conducted to assess the effectiveness of calcium supplementation on the severity of PMS symptoms.

Methods

Research Strategy

This is a systematic review and meta-analysis. The reporting of the manuscript and the preparation of the study protocol were carried out in accordance with the PRISMA statement - checklist for reporting elements in systematic reviews and meta-analysis. The protocol of this study was registered in the PROSPERO database (CRD42022372284). There were no ethics applications, conflicts of interest or funding to report for the conduct of the systematic review and meta-analysis. To minimise the risk of bias in this study, the literature search, selection of articles, data extraction and quality assessment of the articles were carried out separately by two researchers. In case of disagreements and inconsistencies in selection, the opinion of the other researcher was sought and disagreements were resolved through discussion. In addition, in order to complete all stages of the study, all researchers attended a course on systematic review and meta-analysis, in which pilot application and screening stages were carried out on a topic not included in this study.

Selection of Studies

The identification and selection process of the studies to be included in this study was carried out independently by two researchers. The researchers identified the studies based on the inclusion criteria. The researchers analysed the included studies and the repetitive studies were excluded from this study. All included studies were analysed according to title, abstract and full text content. In case of disagreements about the existing studies, all researchers discussed the issue in a session and reached a consensus. PRISMA Flow Diagram Figure 1 shows the selection process of the studies.

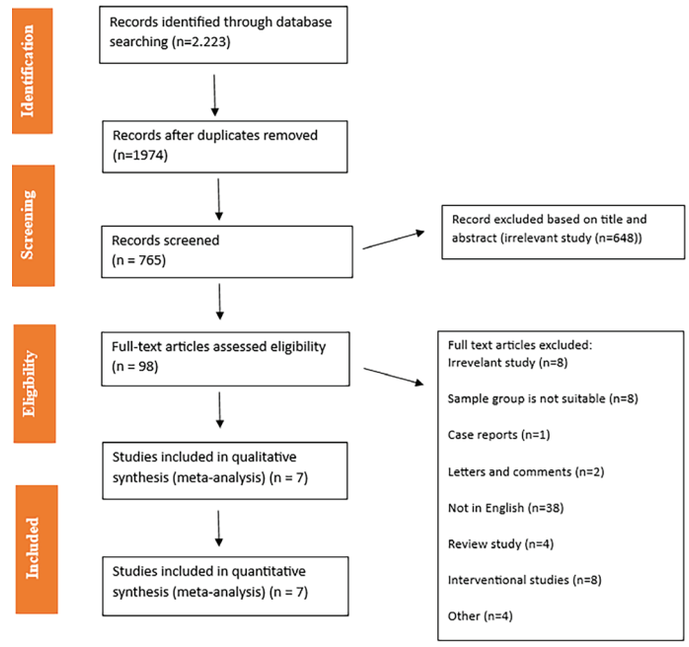

Figure 1 – PRISMA Flow Diagram

Google Scholar, Web of Science, Pubmed and Scopus databases were searched by the researchers between October and December 2022 to conduct this systematic review and meta- analysis study. The keywords "premenstrual syndrome and calcium" and "premenstrual tension and calcium" and "premenstrual dysphoric disorder and calcium" were used to search the databases.

PICOS identified for this study:

Population: Women with Premenstrual Syndrome

Intervention: Calcium and other interventions

Comparison: Placebo

Outcomes: Severity of Premenstrual Symptoms

Study design: Randomised Controlled Trials published in English.

Inclusion criteria;

- Studies published between 2012-2022,
- Randomised Controlled Trials examining the effect of calcium on PMS
- Studies published in English,

Exclusion criteria;

- Studies such as letters to the editor, case reports, papers that are not published as full articles
- Studies whose full text could not be accessed.

Data Extraction

In this review, the researchers used a data extraction tool to obtain the research data. This data extraction tool was used to obtain data about the studies included in the systematic review and meta-analysis, such as where and when the studies were conducted, method, sample size and measurement tool used. Data extraction was performed independently by two authors under the supervision of the third and fourth authors.

All retrieved articles underwent a review process. Duplicate articles were initially excluded. The titles and abstracts of the

remaining studies were read in detail to determine whether they were relevant to this study. The full text of the scanned abstracts and titles was then accessed and carefully reviewed against the inclusion criteria. As a result of the above steps, the articles that met the inclusion criteria were used in the analysis of this study.

Study Quality Assessment

In this review, two authors independently assessed the risk of bias of the studies included in the analysis. The other author performed the review. Disagreements were resolved by discussion between the researchers. The quality of the included trials was assessed using the JBI Critical Appraisal Checklist for Randomised Controlled Trials published by the Joanna Briggs Institute. This checklist consists of 13 items and includes no, yes, not applicable and uncertain responses. In the checklist, items with 'no' and 'unclear' answers received 0 points, while items with 'yes' answers received 1 point. All included studies were analysed, including their titles and abstracts. The full texts of the studies were then examined in the checklist assessment. The scores of the studies are shown in Table 1.

Table 1 JBI Critical Appraisal Checklist For Randomized Controlled Trials Assessment

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Total*
Bharati, 2016	1	0	1	1	0	0	1	1	1	1	1	1	1	**10**
Samieipour, Elahe et al., 2016	1	1	1	1	0	0	1	1	1	1	1	1	1	**11**
Shobeiri et al., 2017	1	1	1	1	1	0	1	1	1	1	1	1	1	12
Yonkers et al., 2013	1	1	1	1	1	0	1	1	1	1	1	1	1	**12**
Yurt et al., 2020	1	1	1	0	0	0	1	1	1	1	1	1	1	**10**
Mandana& Azar, 2014	1	1	1	0	0	0	1	1	1	1	1	1	1	10

*The numbers shown in the columns (1 to 13) are the evaluation items given in the JBI Critical Appraisal Checklist For Randomised Controlled Trials Assessment.

Evaluating the potential of bias

The selected studies underwent risk of bias evaluation in order to produce a quantitative overview of the therapeutic effects of calcium consumption on PMS. Risk of bias was evaluated using the Cochrane risk of bias method for randomized trials (RevMan 5.2.0). Two evaluators worked separately to finalize the assessment after reading the original articles. The final evaluation results were chosen following a discussion about whether the assessors' scores differed.

Statistical Analysis

Data from the trials were coded and analysed using the Comprehensive Meta-Analysis free trial statistical software package (https://www.meta-analysis.com/pages/demo.php). Heterogeneity between studies was assessed using Cochran Q and Higgins I^2 tests, and an I^2' ratio greater than 50% was considered an important indicator of heterogeneity. Random-effects results were considered when I^2' was greater than 50%, and fixed-effects results were considered when the value was lower. For each outcome variable, the 95% confidence interval (CI) was calculated and estimated values were calculated. All tests were calculated as two-tailed. Results were considered statistically significant if the p-value was less than 0.05.

Results

Screening Results

The first stage of the search identified 2223 trials. After eliminating repetitive studies, a selection was made by evaluating the abstracts and titles of the studies. In terms of suitability for our meta-analysis, 117 studies were identified as candidates for inclusion and the full texts of these studies were accessed. The full texts of the studies were analysed. In this study, calcium (n): 187; control (n): 184 sample size and 6 published (Table 2).

Effects of Calcium on Premenstrual Syndrome

In this meta-analysis, calcium-treated experimental groups were compared with non-treated control groups. The standardised difference value of calcium against the control group was calculated as -0.768 (95% CI: -1.255 to -0.281). When calcium administration for the reduction of PMS complaints was compared with the control group, it was determined that calcium reduced the severity of PMS complaints (p=0.002; I2 = 76.2%) (Figure 2). No publication bias was found (Figure 3).

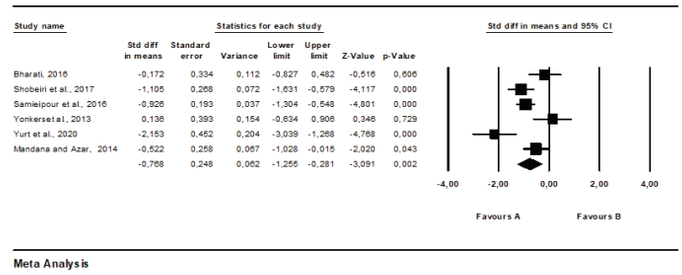

Figure 2 – Forrest graph showing the changes in the severity of PMS complaints between the calcium-administered experimental group and the non-administered control group.

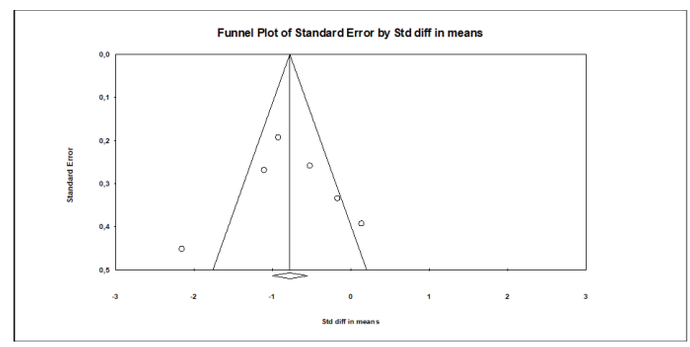

Figure 3 – Bias risk assessment of regarding changes in the severity of PMS complaints between the experimental group given calcium and the control group without calcium

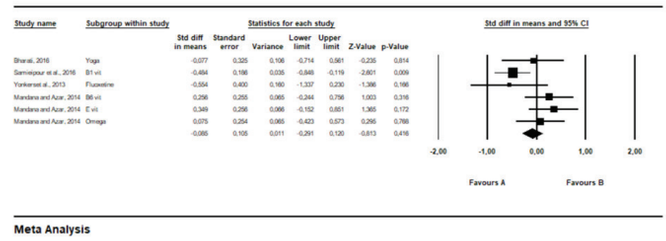

Figure 4 – Forrest graph showing the changes in the severity of PMS complaints between calcium administration and other administrations.

Table 2 Summary of the basics of studies included in the meta-analysis based on the PRISMA method

Author, Year	n	Country	Participants	Intervention group	Control goup	Outcomes	Instrument	Results
Bharati, 2016	65	India	Young female medical students	Yoga group (5 days a week, 1 hour a day, for three months) Calcium carbonate tablet group (500 mg, for three months)	No intervention	Severity of PMS complaints	Questionnaire prepared by researchers	Both interventions reduced PMS symptoms, suggesting that yoga was more effective than calcium supplementation in relieving PMS symptoms.
Samieipour, Elahe et al., 2016	264	Iranian	Students staying in dormitories of Ilam Medical Sciences University	B1 group (100 mg tablet daily, for 2 cycles) Calcium carbonate (500 mg tablet, for 2 cycles) B1+Calcium carbonate (tablet containing 100 mg vitamin B1 + 500 mg calcium carbonate)	Placebo (1gr food starch tablet daily)	Severity of PMS complaints	PMS diagnosis questionnaire	Mean reduction in PMS symptoms in groups Vitamin B1 calcium >Calcium >Vitamin B1>Placebo
Shobeiri et al., 2017	66	Iranian	Female students of Hamadan University of Medical Sciences diagnosed with PMS in 2014	Calcium (500 mg daily, for two months)	Placebo (500 mg starch tablet daily)	Severity of PMS complaints	Daily Record of Severity of Problems scale	A daily intake of 500 mg of calcium is effective in reducing PMS symptoms.
Yonkers et al., 2013	39	USA	Women who meet the inclusion criteria applying for private gynecological examinations in the USA	Fluoxetine group (10 mg twice daily, for four cycles); Calcium carbonate group (600 mg twice daily, for four cycles)	Placebo (placebo tablets that look similar to calcium and fluoxetine tablets)	Severity of PMS complaints	The Inventory of Depressive Symptomatology, Premenstrual Tension Scale, Clinical Global Impression Severity and Improvement scales, and Daily Record of Severity of Problems	Fluoxetine is more effective at reducing premenstrual syndrome symptom severity than calcium.
Yurt et al., 2020	31	Turkish Republıc of Northern Cyprus	The sample consists of voluntary students studying at the Eastern Mediterranean University who meet the study inclusion criteria.	Intervention group (cheddar cheese made from cow's milk (50 g), at least 400 ml of milk and 150 g of yoghurt every day)	No intervention	Severity of PMS complaints	Premenstrual Syndrome Scale (PMSS), the short form of the Quality of Life Scale (SF-36).	Intervention group effective in reducing the severity of PMS
Mandana & Azar, 2014	200	Iranian	All female students of Islamic Azad University Sari branch	Calcium group (1 g calcium per day, for three cycles), Vit E group (100 mg Vit E tablet daily, for three cycles) Omega 3 (1 g capsule fish oil daily, for three cycles), Vit B6 group (40 mg Vit B6 daily, for three cycles)	Placebo (starch tablet)	Severity of PMS complaints	Rosignol Bonlender questionnaire	Vit E, Vit B6, calcium and omega-3 are effective in reducing the severity of PMS

When calcium was compared with some other interventions in the evaluation of the severity of PMS complaints, the standardised difference value was calculated as -0.085 (95% CI: -0.291 to 0.120). The severity of PMS complaints was found to be unchanged when calcium administration was compared with other treatments to reduce PMS complaints (p=0.416; I2 = 54.7% (Figure 4). No publication bias was found (Figure 5).

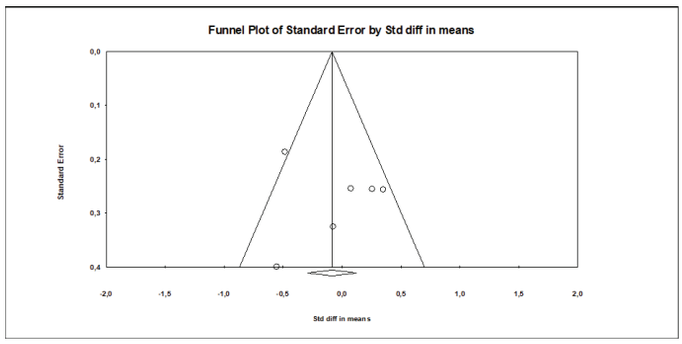

Figure 5 – Bias risk assessment of regarding changes in the severity of PMS complaints between calcium application and other applications.

Discussion

This study is a systematic review and meta-analysis of the effects of calcium on premenstrual symptoms. It included 6 randomised controlled trials that were conducted between 2012 and 2022. There were two main findings from this systematic review and meta-analysis. Calcium was found to reduce the severity of PMS symptoms (p=0.002; I2 = 76.2%) (Figure 2). It was also found that there was no change in the severity of PMS symptoms when calcium was compared with other treatments in reducing the severity of PMS symptoms (p=0.416; I2 = 54.7%) (Figure 4).

The prevalence of PMS was found to be 43%, 52.2%, 53% and 70.8% in systematic reviews and meta-analysis conducted in India, Turkey, Ethiopia and Iran [19–22]. While the prevalence of PMS varies between 19-30% in the USA, it has been reported to be 12% in France and 10% in Switzerland [23, 24]. In a worldwide meta-analysis study by Moghadam et al, the prevalence of PMS was 47.8% [23]. Women who have 12 menstrual cycles per year spend almost 3 months with premenstrual symptoms. This situation reduces women's quality of life and negatively affects their health [25].

Although individualised treatments for PMS symptoms are recommended, PMS symptoms can be treated with non-pharmacological methods (lifestyle changes, cognitive behavioural therapy, dietary supplements), pharmacological methods (chamomile, combined oral contraceptives, serotonin reuptake inhibitors, other psychotropic agents, gonadotropin-releasing hormone analogues) and surgical treatment options [24].

When looking at systematic reviews and meta-analysis studies of treatment options, treatments such as exercise [26, 2], aerobics [27], reflexology [28], yoga [29], aromatherapy [30], chaste herb [31], traditional Chinese medicine [32], dietary supplements and herbal medicines [33], and vitamin D [34] have been found to be effective in reducing PMS symptoms.

Abdi et al investigated the effects of vitamin D and calcium on PMS symptoms and found that calcium and vitamin D supplements could eliminate or reduce PMS symptoms [35]. The study by Arab et al, which investigated the beneficial role of calcium in PMS symptoms, found that calcium may be effective in reducing the incidence of PMS and PMS-related symptoms. [34]. Several studies have shown that women with PMS have low serum calcium levels and that serum calcium levels may reduce the incidence of PMS-related symptoms [36–39]. In a randomised controlled trial conducted by Mandana and Azar, calcium was found to be effective in reducing PMS symptoms [40]. The study by Kermani et al found that PMS symptoms in women who took a combination of calcium and vitamin E decreased and in some cases disappeared [41]. Some studies suggest that vitamin D and high calcium intake may be effective in reducing PMS-related symptoms, including osteoporosis and some cancer risks. Calcium and vitamin D supplementation appears to be an inexpensive, accessible, low-risk and acceptable approach to reducing or eliminating PMS symptoms [42, 34]. ACOG recommends 1.2 mg of calcium supplementation daily to reduce both the physical and psychological symptoms of PMS and to reduce water retention and breast tenderness [31, 43, 44]. In the meta-analysis, calcium supplementation was found to be effective in reducing PMS symptoms. In terms of these results, our study shows similar results to the literature.

In our study, the use of calcium was compared with other applications in reducing PMS symptoms and it was observed that the severity of PMS symptoms did not change with calcium application. In the study by Yonkers et al. comparing fluosectin, calcium and plasebo in the treatment of PMS symptoms, fluosectin was found to be beneficial, whereas the effect of calcium was much less [18]. In a study by Bharati comparing the effects of yoga and oral calcium supplementation in reducing PMS symptoms, it was found that yoga and calcium supplementation were effective in reducing PMS symptoms, but yoga was more effective than calcium supplementation [45].

Conclusion

According to the results of this study, calcium was found to be effective in reducing the severity of PMS symptoms when calcium supplementation was compared with control groups. The use of calcium supplements by women to reduce the severity of PMS symptoms is considered a simple and effective method. In addition, when other treatments for PMS symptoms were compared with calcium, there was no change in the severity of PMS symptoms. More research is needed to compare the effectiveness of other treatments and calcium supplements.

Relevance for clinical practice

Our study shows that calcium supplementation can be recommended as a safe, effective and convenient method to improve patients' quality of life. Nurses working in clinics should consider calcium supplements in their care for individuals experiencing PMS symptoms and inform individuals about calcium supplements.

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Knowledge Level of Patients Undergoing Coronary Angiography

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Abstract

Aim: This study aimed to determine the level of knowledge and related factors of patients undergoing coronary angiography.

Methods: It is a descriptive cross-sectional study. The sample consisted of 256 patients admitted to the cardiology clinic of a training and research hospital for coronary angiography. Data was obtained using the "Patient Information Form" and the "Coronary Angiography Patient Information Form".

Results: Of the patients in the sample, 51.2% were aged 45-59 years. Among those who underwent coronary angiography, 40.6% had a history of previous coronary angiography. A total of 27.3% of the cases reported having stents in their coronary vessels. The majority of the sample (97.7%) was informed by physicians, while the rate of information provided by nurses was 36.4%. The mean total knowledge score of the patients about coronary angiography was 0.65 ± 0.13. There were significant differences in the mean total knowledge scores according to age group, educational level, presence of chronic disease, receiving information about coronary angiography, and the need for information about the angiography procedure ($p<0.05$).

Conclusion: Patients' level of knowledge about coronary angiography is slightly above average and needs to be improved. Moreover, nurses should be more active in patient education and increase their awareness in this field.

Keywords: coronary angiography, coronary artery disease, nurses, patient education

Introduction

Cardiovascular disease, especially coronary artery disease (CAD), is the leading cause of mortality and morbidity worldwide. The World Health Organization (2020) estimates that there were 55.4 million deaths worldwide in 2019 and 17.9% of these deaths were due to CAD [1]. According to the Turkish Statistical Institute (2019), circulatory system diseases are the most common cause of death with a rate of 36.8%. Among circulatory system diseases, ischemic heart disease (39.1%) is ranked first [2]. Combined with further advances in technology, medical and surgical methods are used to reduce the mortality and morbidity of CAD. The most accurate of diagnostic methods is coronary angiography (CAG), which is considered the gold standard among interventional therapies for clinical diagnosis [3-5]. Coronary angiography is a minimally invasive intervention in which special wires are advanced into the coronary arteries through special catheters inserted into the peripheral arteries and a radio-opaque substance is administered to visualize the coronary arteries fluoroscopically under x-rays [6, 7].

Improvements in CAG have made it a preferred choice for patients due to its feasibility, shorter and easier procedure [8, 9]. Some patients may not consider CAG a serious operation, and patients who will undergo CAG for the first time generally believe that their heart disease will disappear and their treatment will be completed after the procedure based on their knowledge acquired from written, oral, and visual media forms. Even if some patients who have had this intervention before may be experienced to a certain extent, they may make errors in adhering to post-procedural self-care guidelines in the hospital environment after the intervention and in-home care after discharge [10]. Coronary angiography is an invasive procedure that causes complications as well as being a widely used method in the diagnosis and treatment of CAD. Vascular problems are usually encountered at the CAG site. These complications include hematomas, bleeding, arteriovenous fistula, pseudoaneurysm, arterial occlusion, retroperitoneal

hematomas, cardiac arrhythmia, femoral neuropathy, contrast agent allergy, and infections. In addition, excessive use of radiopaque material also increases the rate of renal failure [11, 12]. Additionally, some patients may experience stress, anxiety, depression and fear of death for various reasons before invasive interventions such as CAG [13, 14]. Mild anxiety before CAG is common among patients. However, when it reaches the level of severe anxiety, patient outcomes such as prolonged hospital stay, refusal of procedure, and cardiac events may be negatively affected. Some factors that may cause anxiety in patients include the waiting time for CAG, stress about the outcome of angiography, fear of the cardiac catheterization unit, and a complication of angiography. Furthermore, the most common cause of anxiety is poor knowledge of the angiography procedure. An assessment of the level of knowledge and anxiety of the patient before angiography is one of the important responsibilities of healthcare professionals [15]. In fact, a significant relationship was found between patients' the level of knowledge about angiography and anxiety levels in patients undergoing CAG [15–17].

Although CAG is the most reliable method used for visualization of coronary arteries, it carries risks such as vascular complications, infections and increased anxiety in patients. Nurses involved in the care of individuals undergoing CAG play an active role in managing the diagnosis and treatment of patients at risk with a healthy process and improving clinical outcomes with patient education. While coronary angiography should be regarded in its entirety as a whole procedure, nursing interventions before, during, and after the procedure should be handled separately [12, 18]. Therefore, before the CAG, nurses should inform patients by taking into consideration various factors such as the patient's age, gender, educational status, anxiety, and level of knowledge about the disease [18–20]. Patient education, prevention, early diagnosis, and intervention of complications that may occur after CAG are possible through increased awareness, adequate theoretical knowledge and experienced nursing care [21]. This study was conducted to evaluate the level of knowledge of patients undergoing CAG and to determine the relevant factors, which are important given the increasing use of CAG in the diagnosis and treatment of CAD.

Methods

Study Design and Setting

This is a descriptive cross-sectional study. The study was carried out on patients who planned to undergo CAG in the cardiology department of a training and research hospital in Istanbul.

Population and Sample

The population consisted of outpatients and inpatients who came in to the cardiology clinic of the hospital and underwent CAG between January and March 2021. The sample calculation is based on the number of patients in 2020 during the period of the study. The sample size was determined using the sample size formula with a known population. At least 214 patients would have to be included in the sample for a population of 1018 with a confidence interval of 90% with a margin of error of alpha 0.05, and the study was conducted with 256 patients. The sampling criteria were patients who were treated as outpatients or inpatients for CAD for the duration of the study, were 18 years of age or older, could read and speak Turkish, had no communication problems, and had agreed to participate in the study.

Data Collection

The questionnaire forms were given to the patients before the procedure, and the patients were asked to fill them in. The purpose and method of the study was explained to the patients, they were told that it would take 15-20 minutes to fill out the forms and written informed consent was obtained from the patients. Data was collected using the Patient Information Form and Coronary Angiography Patient Information Form.

Patient Information Form: The form was prepared by the researcher following the literature review [10, 22, 23] and included questions about the descriptive and clinical characteristics of the patients.

Coronary Angiography Patient Information Form: This form was created by the researchers in line with the literature [10, 20, 23, 24]. The form consists of 25 questions about matters for consideration before and after CAG. Correct answers to the statements in the information form were scored as "1" point and incorrect answers were scored as "0" points. Items 3, 4, 6, 7, 9, 16, and 22 were reversed and scored as they contained incorrect statements. The mean scores of the patients' responses to each item ranged between "0" and "1" points. The total score of the information form consists of the sum of the average score given to each item. A total score closer to 1 indicates that the patient has more knowledge about CAG.

The items in the questionnaire form were presented to two cardiology physicians and two academics in the field of internal medicine nursing for examination in terms of comprehensibility, readability, and expressiveness, and expert opinions and suggestions were obtained. After receiving their opinions, a pilot study was conducted on 10 patients. Following the pilot study, the items were found to be appropriate in terms of comprehensibility and applicability. The 10 patients included in the pilot study were excluded from the scope of the study. The internal consistency coefficient of the patients' responses to the information form was calculated with Kuder-Richardson Formula 20 (KR-20) (KR = 0.632).

Data Analysis

For data analysis, the IBM 21.0 (Statistical Package for Social Sciences IBM Corp., Armonk, NYC, USA) statistical program was used. A normal distribution was accepted if the Kurtosis and Skewness values obtained from the intra-item scales were between +3 and -3. According to the variables with two groups, the difference between the total knowledge scores was analyzed with t-test and the difference between the variables with three or more groups was analyzed with the ANOVA test.

Ethics Consideration

The ethics committee approval was received from the Non-Interventional Research Ethics Committee with the decision dated 30.11.2020 with number 2020/45-04, and following this, permission was then obtained from the hospital where the study was conducted. Informed written consent was obtained from patients who agreed to participate in the study. This study was conducted in accordance with the Declaration of Helsinki.

Results

Descriptive and Clinical Characteristics of the Patients

The age range of the patients was 45-49 years (51.2%) and 58.6% were male. The majority of patients were married (85.9%), had graduated from primary school (45.3%), and had income equal to expenses (37.9%). Of the patients, 71.9% had chronic diseases, 56.3% had hypertension, and 40.6% had previously undergone CAG. It was determined that 14.1% of the patients had undergone angiography once before and 27.3% had a stent implantation in the heart. The rate of patients informed about CAG by physicians and nurses was 97.7% and 36.4%, respectively (Table 1).

Table 1 Descriptive and clinical characteristics of patients (N=256)

Characteristics		n	%
Age	18-44	39	15.2
	45-64	131	51.2
	Over 65 years old	86	33.6
Gender	Male	150	58.6
	Woman	106	41.4
Marital status	Married	220	85.9
	Single	36	14.1
Educational level	Primary school	116	45.3
	Middle school	27	10.5
	High school	63	24.6
	Graduate	35	13.7
	Postgraduate	15	5.9
Employment status	Working	122	47.7
	Not working	134	52.3
Profession	Worker	29	11..3
	Officer	42	16.4
	Self-employment	21	8.2
	Retired	64	25.0
	Housewife	57	22.3
	Not working	43	16.8
Income status	Income less than expenditure	75	29.3
	Income equal to expenditure	97	37.9
	Income more than expenditure	84	32.8
Cigarette use	Yes	136	53.1
	No	120	46.9
Duration of smoking (n=136)	Using for 0-5 years	2	0.8
	5-10 years of use	9	3.5
	10-20 years of use	20	7.8
	More than 20 years of use	105	41.0
Alcohol use	Yes	41	16.0
	No	215	84.0
Presence of chronic disease	Yes	184	71.9
	No	72	28.1
*If yes	Hypertension	144	56.3
	COPD-asthma	28	10.9
	Diabetes	89	34.8
	Heart disease	65	25.4
	Other chronic diseases	63	24.6
Previous CAG procedure	Yes	104	40.6
	No	152	59.4
Number of CAG (n=104)	1 time	36	14.1
	2 times	32	12.5
	3 times	20	7.8
	4 times or more	16	6.3
Stent presence	Yes	70	27.3
	No	186	72.7
Education about coronary angiography	Yes	92	35.9
	No	164	64.1
*Information received from whom about CAG procedure	I learned from my close circle	138	53.9
	I learned from the internet, social media, television	77	30.1
	I was informed by the physician	250	97.7
	I was informed by the nurse	93	36.4
Need for information about coronary angiography	Yes	211	82.4
	No	45	17.6
*If yes Subjects you would like to receive information about	I would like information about what to do before the procedure	88	34.4
	I would like to get information about the subjects that I should pay attention to after the procedure	183	71.5
	Others (post-procedure patient follow-up, access to health workers, etc.)	60	23.4

**means more than one option can be marked; CAG: Coronary angiography*

Table 2 Distribution of responses to the Coronary Angiography Patient Information Form

	Incorrect Answer		Correct Answer		Mean	SS
	n	%	n	%		
1. Coronary angiography is a diagnostic intervention to identify a blockage in a blood vessel.	3	1.2	253	98.8	0.99	0.11
2. Coronary angiography is an intervention to place a stent in the patient's vessel.	202	78.9	54	21.1	0.21	0.41
3. During the intervention, general anesthesia should be applied and the patient should be put to sleep.	72	28.1	184	71.9	0.72	0.45
4. It is an intervention performed only through the groin.	132	51.6	124	48.4	0.48	0.50
5. Radio-opaque material is given during the intervention.	97	37.9	159	62.1	0.62	0.49
6. During the intervention, the patient's blocked veins are cleared.	177	69.1	79	30.9	0.31	0.46
7. Hospitalization is required one day before the intervention.	120	46.9	136	53.1	0.53	0.50
8. Fasting 4-6 hours before the intervention is sufficient.	60	23.4	196	76.6	0.77	0.42
9. Fluid/water intake should be stopped 4-6 hours before the intervention.	194	75.8	62	24.2	0.24	0.43
10. The groin is shaved before the intervention.	12	4.7	244	95.3	0.95	0.21
11. Electrocardiography, doctor's orders, laboratory results, medications and surgery reports, if any, should be brought to the intervention.	7	2.7	249	97.3	0.97	0.16
12. Surgical clothes are put on before the intervention.	0	0.0	256	100	1.00	0.00
13. Coronary angiography is an intervention that takes as little as 15-45 minutes.	32	12.5	224	87.5	0.88	0.33
14. In the post-processing zone a sandbag is placed to stop the bleeding.	11	4.3	245	95.7	0.96	0.20
15. Hospitalization is not required after the intervention.	156	60.9	100	39.1	0.39	0.49
16. Food is not eaten or consumed immediately after the intervention.	50	19.5	206	80.5	0.80	0.40
17. At least 2.5-3 liters of water should be consumed after the intervention.	15	5.9	241	94.1	0.94	0.24
18. Bed rest is required for 4-6 hours after the intervention.	15	5.9	241	94.1	0.94	0.24
19. There may be bleeding, swelling, etc. in the intervention area after the intervention.	76	29.7	180	70.3	0.70	0.46
20. Nausea, vomiting, dizziness, headache,weakness, and chest pain may occur after the intervention.	89	34.8	167	65.2	0.65	0.48
21. After the intervention, fluid intake and urine are monitored.	144	56.3	112	43.8	0.44	0.50
22. All cardiac disorders disappear after the intervention.	155	60.5	101	39.5	0.39	0.49
23. You can shower/bath 24 hours after the intervention.	170	66.4	86	33.6	0.34	0.47
24. Driving, sports, etccan be done immediately after the intervention	118	46.1	138	53.9	0.54	0.50
25. Return to routine life 24 hours after the intervention.	135	52.7	121	47.3	0.47	0.50
Coronary Angiography Patient Information Form	**X̄ ± SD Min Max**					
Total Score	0.65 ±0.13 0.36 0.96					

SD: Standard deviation

Table 3 Comparison of Coronary Angiography Patient Information Form in terms of patients' characteristics

Variables		Partiscipants	Coronary Angiography Patient Information Form	t/F	p
		n (%)	Ort±Sd		
Age	30-44 years[1]	39 (15.2)	0.71 ± 0.11	F: 13.609	**0.000*** 1>3; 2>3
	45-64 years[2]	131 (51.2)	0.66 ± 0.13		
	65 years and older[3]	86 (33.6)	0.60 ± 0.11		
Gender	Male	150 (58.6)	0.66 ± 0.13	t: 0.866	0.387
	Woman	106 (41.4)	0.64 ± 0.13		
Education	Primary school[1]	116 (45.3)	0.61 ± 0.11	F: 17.626	**0.000*** 1<4; 1<5; 2<4; 2<5 3<4; 3<5
	Middle school[2]	27 (10.5)	0.60 ± 0.10		
	High school[3]	63 (24.6)	0.65 ± 0.11		
	Graduate[4]	35 (13.7)	0.77 ± 0.11		
	Postgraduate[5]	35 (5.9)	0.74 ± 0.14		
Chronic disease	Yes	184 (71.9)	0.64 ± 0.13	t: -2.277	**0.024***
	No	72 (28.1)	0.68 ± 0.12		
Having had a CAG before	Yes	104 (40.6)	0.64 ± 0.12	t: -1.090	0.277
	No	152 (59.4)	0.66 ± 0.12		
Number of CAG	1	36 (14.1)	0.66 ± 0.14	F: 1.358	0.260
	2	32 (12.5)	0.65 ± 0.11		
	3	20 (7.8)	0.60 ± 0.11		
	≥ 4	16 (6.3)	0.62 ± 0.11		
Education about CAG	Yes	92 (35.9)	0.70 ± 0.12	t: 5.297	**0.000***
	No	164 (64.1)	0.62 ± 0.12		
Need for information about CAG	Yes	211 (82.4)	0.70 ± 0.12	t: 3.043	**0.003***
	No	45 (17.6)	0.62 ± 0.12		

*CAG: Coronary angiography; F: ANOVA test; t: t test; *p<0.05*

Coronary Angiography Patient Information Form Scores

Analyzing the responses of the patients to the items of the information form, it was determined that they gave the most correct answers to the items "Surgical clothes are put on before the intervention (100%)", "Coronary angiography is a diagnostic intervention to identify a blockage in a blood vessel (98.8%)", "Electrocardiography, doctor's orders, laboratory results, medications and surgery reports, if any, should be brought to the intervention (97.3%)". The items to which the patients gave the least correct answers were "Coronary angiography is an intervention to place a stent in the patient's vessel" (21.1%), "Fluid/water intake should be stopped 4-6 hours before the intervention" (24.2%), and "During the intervention, the patient's blocked veins are cleared" (30.9%). According to the responses given by the patients, the mean total knowledge score for CAG was 0.65±0.13 (Table 2).

Comparison of Information Form Score Averages According to Descriptive and Clinical Characteristics of Patients

There was a statistically significant difference between the age groups in terms of total knowledge score ($p<0.05$). The results showed that the mean knowledge score of those aged 30-44 was the highest. A weak, negative ($r=-0.289$) and significant relationship was found between the age groups of the patients and the Coronary Angiography Knowledge Form score ($p<0.01$). Compared to the groups with different levels of education, total knowledge score showed a significant difference ($p<0.05$). Per these results, the mean knowledge score of those with bachelor's and master's degrees was higher than those with primary, secondary, and high school degrees. The difference in total knowledge score between the groups with chronic disease was statistically significant ($p<0.05$). For those without chronic disease, the mean knowledge score was higher than the mean knowledge score of those with chronic disease. A statistically significant difference was found between the total knowledge scores of patients who received education about CAG ($p<0.05$). The mean knowledge scores of patients who received training about CAG were higher than those who did not receive training (Table 3).

Discussion

As with any invasive procedure, the CAG procedure may lead to some complications. Information provided to patients before CAG may prevent psychological problems as well as physiological complications. Therefore, evaluating the knowledge level of the patients and providing education in line with their needs could be important in terms of the effectiveness and applicability of the education and patient care outcomes. The present study addresses this important aspect of patient care and emphasizes the need to improve educational efforts, particularly for nursing staff. The study also presents areas for improvement in patient education and care in the context of CAG and suggestions for increasing nurse involvement in patient education.

Discussion of Findings Related to Coronary Angiography Patient Knowledge Score

Patient education is one of the most important dimensions of patient-centered care. Determining which subjects patients want to be informed about and prioritizing them can make education more effective and efficient. Organizing patient education according to the information needs of patients may contribute positively to the expected patient care outcomes and increase patient satisfaction and nursing care quality [25, 26]. In this study, the mean total knowledge score obtained in the study was 0.65 ± 0.13. As the minimum score obtained from the form is 1 and the maximum score is 5, it can be concluded that the total knowledge score of patients is slightly above the average value (0.5). This shows that the level of knowledge of the patients regarding CAG should be improved. The study by Shaheen et al. reported that patients did not have adequate knowledge about CAG, with only 6% patients having good knowledge, 42% moderate and 52% poor knowledge [15]. In some studies, the patients were found to have poor knowledge before the intervention, while the education offered to the patient after the intervention, that is, before cardiac catheterization, increased the knowledge score [16, 17, 27]. Post-angiography individuals may need education on many subjects to adapt to the new situation and develop effective coping behaviors. However, some patients may need less information, while others may not want to receive too much information because they do not need it. Missing or incorrect information can lead to different interpretations or perceptions of the importance of information, while too much information can lead to cognitive overload in patients. Due to this overload, patients may forget the information they have received or feel more stressed. Therefore, the first step in meeting individual information needs is to identify and understand them. The results of the assessment may provide important data for planning treatment and care in line with patient needs.

Regarding some items obtained from the Coronary Angiography Patient Information Form, 51.6% of the patients stated that CAG was performed only through the inguinal region. In the study of Yılmaz et al. [28], 77.1% of the patients answered the question from which vein the CAG was performed from the inguinal vein [28]. CAG is performed by using brachial arteries with the Sones method and femoral arteries and radial arteries with the Judkins (Seldinger) method [27, 29]. Although the most appropriate decision in this regard is made together with the physician according to the patient's condition, patients should be informed in detail about the types of CAG methods.

In the Coronary Angiography Patient Information Form, 76.6% of the patients responded correctly to the item that it is sufficient to fast for 4-6 hours before the procedure, and the correct response rate to the item that water/liquid intake should be stopped 4-6 hours before the procedure was 24.2%. According to the 2011 guidelines of the American Society of Anesthesiologists, the patient's oral intake should be terminated at least 4-6 hours before the CAG, while fluid intake can be continued up to 2 hours before the intervention [30].

In the Information Form, 95.7% of the patients gave the correct answer to the item "A sandbag is placed to stop bleeding in the intervention site after CAG". After CAG, the intervention site of the patients is closed by applying a tight bandage and tampon. Following taking the patient's to bed, a sandbag is placed on the site where the intervention was performed and the location is observed for bleeding [31, 32]. However, with advancing and developing technology, observation of the intervention site in terms of bleeding has become more practical. Hemostasis of the intervention site can be performed with special closure devices without the need for sandbags, tight tampons, and bandages. But since these devices are not widely used or preferred in practice, sandbagging is the most common method to stop bleeding.

In the study, 56.3% of the patients gave incorrect answers to the item "Fluid intake and urine are monitored after the CAG". In the Nursing Guideline published by the Turkish Society of Cardiology in 2007, the patient's intake is monitored with oral intake after CAG. Since a contrast radio-opaque substance that facilitates the visualization of coronary arteries is given during the intervention, the patient's fluid intake is encouraged and monitored to prevent dehydration and nephropathy that may be caused by the contrast material in the patient after the intervention. In this way, the removal of the contrast material from the body is accelerated. Intravenous fluid intake and blood transfusion

are provided according to the physician's order and the patient is observed every hour and recorded on the patient observation form [33]. Of the patients, 60.5% gave an incorrect answer to the item "All cardiac disorders disappear after CAG". Incorrect answers were given by 66.4% of the patients to the item that a shower/bath can be taken 24 hours after the intervention, 46.1% to the item that driving, sports, etc. can be done immediately after the intervention and 52.7% to the item that routine life can be resumed 24 hours after the intervention. Education contributes to making changes in the lifestyle of the patients, developing appropriate coping methods in their adaptation to the disease, and increasing their comfort levels [24]. As such, the patient can return to their homes or to their usual social environments after the procedure. The intervention site should be observed by the patient or his/her relatives for at least 24 hours after leaving the hospital. In case of bleeding, swelling, or redness, the nearest health institution should be consulted. The patient can take a shower with a warm bath 24 hours after the intervention without rubbing the site of the intervention and without keeping it too hot. The patient can drive after the intervention but should avoid fast and sudden foot movements, activities that will use excessive force and effort, and protect the intervention site from impacts. The patients should be told that they can do sports, exercise, and go on daily walks at a light pace 24 hours after the intervention [23, 31, 34].

In this study, the nurses were significantly more behind than physicians in angiography education. One reason for physicians to take part in more training on angiography is that physicians may also provide information while recommending this procedure to the patient. Likewise, in a study conducted by Şatıroğlu et al. [10], the majority of patients (77%) stated that they had been informed about CAG by physicians and half of the patients (50.7%) they found the information provided by physicians sufficient. In a different study [16], patients' source of information was mostly physicians (87%), but the majority of participants reported that this information was inadequate. With that in mind, providing in-house in-service trainings to increase the awareness of nurses on this issue is very important. Studies show that nurses received in-service training on the care of patients undergoing cardiac catheterization procedures and found their level of knowledge sufficient [11] or that the participants' in-service training was not at the desired level [35].

Discussion of the findings related to the comparison of information form scores according to the descriptive and clinical characteristics of the patients

With the development of science and technology, CAG has become practical. The patient undergoing the procedure is both diagnosed and treated with stents and angioplasty in the same session, except for elective conditions [36, 37]. In this study, more than half of the patients reported that they had not previously undergone CAG. Similarly, in Gören's study [38], the rate of those that did not have a previous CAG was 51.6%, while this rate was 63.72% in the study of Yılmaz et al. [23]. In our study, no statistically significant difference was found when the knowledge scores of individuals who stated that they had previously undergone CAG were compared with individuals who had not undergone CAG. It is expected that patients who have had previous CAG have higher knowledge levels than those who have not. However, education should be repeated even if patients have previous experience. Previous training may not have been effective and sufficient, and patients may not have understood or may have forgotten. In a study [10], it was reported that patients who will undergo CAG for the first time may "simplify" the procedure and may think that all cardiovascular diseases will be eliminated or that their treatment will be completed after the intervention with the information they have heard and seen from their close environment or as a result of their research in written oral and visual media.

In this study, 98.2% of the participants stated that the CAG is a diagnostic method, while the same participants responded that CAG is an application in which a stent is placed with 21% in another question. In the study conducted by Şatıroğlu et al. [10], the rate of those who responded correctly that CAG was a diagnostic procedure for CAD was 36%, and the rate of those who said that their disease would be treated and the heart vessel would be opened was 32%. In the study by Yılmaz et al. [28], 44% of the patients responded to the question of the purpose of CAG as visualization of the vessels and 37% as opening of the vessels. In the same study, it was stated that fear of surgery, incorrect or incomplete information, and uncontrollable anxiety of the individual may affect the individual's compliance with diagnosis and treatment [28]. Considering the results, individuals know what CAG is, but they lack information about the purpose of the procedure.

In the current study, the mean scores of those who needed information about CAG and those who received education on this subject were found to be higher, which is expected. Those who want to be informed may have done more research or their willingness to learn may be higher than others. Education is the best process realized in line with the individual's teaching-learning process. This is a way in which the desired behaviors can be taught to the individual and those around him/her most easily. Patient education is the basis of nursing interventions before, during, and after the CAG procedure. It was found that the mean scores of those who needed information about CAG and those who received training on this subject were higher, which is expected [19]. Balcı and Enç [13] found that audio-visual (video) training given before CAG had a positive effect on physiological and psychosocial parameters after the procedure. The World Health Organization Regional Office for Europe drew attention to the importance of health education in achieving the "Health for All Goals" and emphasized that all nurses are health educators. The responsibility of nurses for patient education has also been emphasized in the reports of national and international studies and the laws and regulations related to nursing. All these developments have led nursing to take a professional educational role [39]. It is very important to plan patient education considering age, gender, and educational level. Particularly when it comes to imaging and diagnosis or treatment of a vital organ such as the heart with a minimally invasive procedure such as CAG, it is important to plan by paying attention to these [23].

In addition to diagnosis and treatment, health perception and disease management are very important in cardiovascular diseases. External factors that individuals experience in accessing information greatly affect the disease and the individual. Studies show that individuals aged 40 years and older are exposed to a higher risk of CAD with advancing age [22, 40, 41]. When the responses of the age groups to the CAD information form were compared, statistically significant differences were found in total information scores. With increasing age, the need for information is higher in individuals. It may be related to the increasing needs of individuals and their dependency on others. In addition, with the death of one of the spouses, patients may be left alone. This may have increased the patients' awareness of their diseases or current problems. In the study, the total knowledge score of individuals who did not have a chronic disease was found to be higher. Individuals who do not have chronic diseases may need more information because they have not experienced such problems before. This study shows that the mean knowledge score of patients with higher education was higher than the others.

As a result of advancing age and emerging chronic diseases,

people encounter more problems due to the weakening of the immune system, adaptation difficulties, and problems in coping with stress. These bring on not only biological and physical, but also mental and social problems [42]. Similarly, participants aged between 31 and 60 years had good knowledge, while participants older than 60 years had poor knowledge. Also, a significant association was found showing that educated participants had good knowledge compared to illiterate participants [16].

Limitations

This study was conducted in a public hospital. Therefore, the results of this study cannot be generalized to all patients with CAD. A larger sample size in public and private hospitals is recommended for future studies. In addition, the information form is limited to the knowledge and practices related to CAD developed by the researcher.

Conclusion

Patients' level of knowledge about CAG procedures is above the mean value. The rate of patients being informed about CAG by nurses is lower than that of physicians. As the age increases, the mean knowledge score of the patients decreases. According to the results of the study, the mean knowledge scores of patients with a bachelor's degree, patients without chronic diseases, and patients who need information about the procedure are higher. In addition, the mean score of those who received education about CAG was also found to be higher.

There is a need to increase and improve the level of knowledge of patients about CAG. In patient education, it is important to use patient-appropriate education methods and to repeat/update information even if the patients have been previously informed or have knowledge on the subject. Moreover, the awareness of nurses working in cardiology services, coronary intensive care units, and angiography laboratories of healthcare institutions about patient education related to CAG should be increased. In planning the training to be given to the patient, the individual characteristics of the patient should be taken into consideration, and educational needs should be determined. Additionally, nurses should have qualified and sufficient knowledge about both the care and interventional practices of patients planned for CAG and should be able to evaluate the results of these practices on the patient.

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Relationship between the Coronary Slow Flow Phenomenon and the Vertebrobasilar Insufficiency

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Abstract

Background: Coronary slow flow phenomenon (CSFP) and vertebrobasilar insufficiency (VBI) may have common pathophysiological mechanism.

Aim: Our aim was to investigate whether there is an association between vertebrobasilar flow assessed by Doppler sonography and CSFP assessed by Thrombolysis in Myocardial Infarction (TIMI) frame count.

Methods: We included 241 patients who had CSFP and underwent vertebrobasilar Doppler sonography. Patients with vertebral artery blood flow volumes greater than 200 ml/min and equal to or less than 200 ml/min were classified into the normal flow and low flow groups, respectively. Hospital records were used to determine the biochemical and demographic characteristics of the patients.

Results: The mean age of the study population was 58.75±9.34 years. We found no differences between patients with normal and low vertebral blood flow in terms of age, sex, body mass index, smoking habit, presence of hypertension, hyperlipidemia, diabetes mellitus or medication use. Patients with low vertebral blood flow were found to have greater mean platelet volume. The mean TIMI frame count and LAD, Cx, and RCA TIMI frame counts were significantly greater in patients with low vertebral blood flow and were negatively correlated with the vertebral artery blood flow volume ($p<0.001$ for all). A mean TIMI frame count of 24.5 predicted VBI, with a sensitivity and specificity of 61.2% and 86.8%, respectively. The only predictor of VBI was the mean TIMI frame count (OR: 1.066, 95% confidence interval: 1.043–1.091, $P<0.001$).

Conclusion: Our findings suggest that a common pathophysiological mechanism may underlie both CSFP and VBI.

Keywords: Coronary, slow flow, vertebrobasilar, flow.

Introduction

The term vertebrobasilar insufficiency (VBI) is used to describe a clinical syndrome in which there is decreased blood flow in one or more vessels of the vertebrobasilar circulation. The vertebral and basilar arteries supply blood to the posterior part of the brain, including the cerebellum, spinal cord, occipital cortex, and midbrain. Reduced blood flow to these arteries results in a variety of symptoms, including dizziness, syncope, drop attacks, confusion, and visual, auditory and cardiac problems [1]. Symptoms vary depending on the part of the brain affected. Elderly and diabetic patients are particularly affected by reduced perfusion, resulting in ischemia. The main cause of VBI is atherosclerosis, and the progression of atherosclerotic plaques over time can cause ischemic events [2]. Risk factors involved in the pathogenesis of atherosclerosis may predispose patients to VBI. Patients diagnosed with coronary or peripheral arterial disease are at risk for VBI. Like atherosclerotic disease, its prevalence increases with age and tends to affect men. In addition to atherosclerosis, embolic events and compressive effects of cervical spondylosis are other factors that cause VBI [3].

The coronary slow flow phenomenon (CSFP) is an angiographically described entity associated with the sluggish passage of contrast agent within coronary arteries without significant obstruction. It is found in 1 to 7% of patients undergoing coronary angiography and has been reported in up to one-third of patients with anatomically normal coronary arteries [4]. Since it may be the cause of ischemic symptoms, it may have a negative impact on the patient's life. Although the pathophysiological abnormalities underlying coronary slow flow are not well understood, an imbalance between the vasoconstrictive and vasodilator effects of substances secreted by the endothelium is among the suggested possible mechanisms of this phenomenon [5]. CSFP tend to occur in males, smokers, and those with characteristics of metabolic syndrome [6]. Caiati et al. reported that CSFP does not occur without atherosclerotic involvement of the coronary microvasculature, suggesting that it may be an early stage of atherosclerosis [7].

On the basis of the hypothesis that CSFP and VBI may have a common pathogenesis, we investigated the connection between vertebrobasilar flow assessed by Doppler sonography and CSFP assessed by Thrombolysis in Myocardial Infarction (TIMI) frame count.

Materials and methods

The study was retrospective in design. Five thousand seven hundred and twelve patients who underwent coronary angiographic examination at a tertiary hospital clinic between July 2016 and March 2022 were screened. Among these patients, 603 patients with CSFP were selected. Patients were considered acceptable for the study if they underwent vertebrobasilar Doppler sonography within six months prior to or following an angiography procedure. Patients with heart failure, subclavian steel syndrome, a hypoplastic vertebral artery, more than 50% occlusion in either the vertebral or coronary artery or vertebral artery stenosis, valvular heart disease, a history of cerebrovascular accidents, or acute infection were not included in the study. Two hundred forty-one patients remained and were included in the study. The study protocol complied with the ethical standards of the 1964 Declaration of Helsinki and was approved by the hospital ethics committee. Informed consent was obtained from patients prior to enrollment.

Blood samples for biochemical and complete blood count analyses were obtained from each patient after a 12-hour fast.

Doppler sonographic examinations of the patients were performed from the C4 and C5 intertransverse segments at an angle of less than 60 degrees via a Samsung RS80 EVO (Samsung Medison, Seoul, Korea) with a 3–12 MHz transducer. All measurements were performed with the patients at rest for ten minutes and in the supine position. Both vertebral arteries were evaluated from the level of the orifice to the base of the skull, and flow sampling was performed. The average of three measurements of blood flow volume (ml/min) was obtained from the right and left vertebral arteries of each patient. The net vertebral artery blood flow volume was obtained by averaging the right and left vertebral artery blood flow volumes. Patients were split into two groups according to their vertebral artery blood flow volumes. Patients with vertebral artery blood flow volumes greater than 200 ml/min or equal to or less than 200 ml/min were classified into the normal-flow or low-flow group, respectively.

The coronary angiograms of the study patients were interpreted by an interventional cardiologist who was aware of the patients' clinical information. The epicardial blood flow of the patients was classified into four groups according to the TIMI system [8]. The diagnosis of CSFP was made via the TIMI frame count method, in which the first frame is considered the moment when the coronary artery ostium is fully stained with a dying agent, and the last frame is considered the moment when the distal point of the relevant artery is filled with the dying agent [9]. The distal reference points of the left anterior descending artery (LAD), circumflex artery (Cx), and right coronary artery (RCA) are accepted as the terminal bifurcations of the LAD and Cx and the first branch of the posterolateral artery of the RCA, respectively. The corrected LAD TIMI frame count was calculated by dividing the TIMI frame count by 1.7. The mean TIMI frame count was calculated by adding the LAD, Cx, and RCA TIMI frame counts and dividing the result by three.

Statistical analysis

The normality of the data was assessed by analyzing the skewness and kurtosis of the data. Quantitative data from the two groups were examined via independent samples t tests or Mann–Whitney U tests. The differences in the qualitative data were determined via the chi-square test. The correlations of vertebral artery blood flow volume with TIMI frame counts were determined via Spearman correlation analysis. The cutoff value of the mean TIMI frame count for the VBI was calculated via receiver operating characteristic (ROC) curve analysis. Univariate logistic regression analysis was performed to evaluate the independent predictors of the VBI. Significantly different variables were included in the multivariate logistic regression analysis. A p value less than 0.05 was considered significant.

Results

The average age of the study population was 58.75±9.34 years, and the mean body mass index was 29.21±5.88 kg/m2. Among these patients, 126 (52.3%) were male, 65 (27%) had diabetes mellitus, 148 (61.4%) had hypertension, and 87 (36.1%) had hyperlipidemia. We found no differences between patients with normal and low vertebral blood flow with respect to age, sex, body mass index, smoking habit, or the presence of hypertension, hyperlipidemia, or diabetes mellitus. In addition, there were no differences between medication use and biochemical variables, except for the mean platelet volume, which was greater in patients with low vertebral blood flow. The mean TIMI frame count and LAD, Cx, and RCA TIMI frame counts were significantly greater in subjects with low vertebral blood flow. Table 1 and Figure 1 show the biochemical and clinical variables and the mean TIMI frame counts of the two groups.

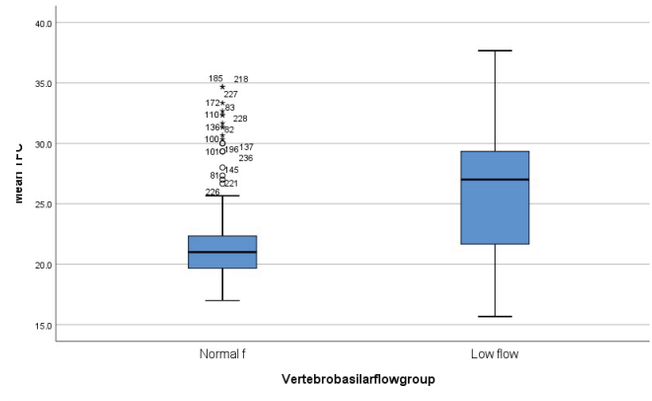

Figure 1 – TIMI frame counts of the two groups

Table 1 Clinical and biochemical variables of the two groups.

	Normal flow group (n=174)	Low flow group (n=67)	p
Age (years)	58.02±9.51	60.63±8.68	0.053
BMI (kg/m2)	28.68 (27.78-33.37)	29.38 (26.44-35.54)	0.231
Gender (n, %)			0.253
Male	87 (50)	28 (41.8)	
Female	87 (50)	39 (58.2)	
Smoking (n, %)	83 (47.7)	34 (50.7)	0.672
COPD (n, %)	31 (17.8)	18 (26.9)	0.125
Diabetes mellitus (n, %)	50 (28.7)	15 (22.4)	0.320
Hypertension (n, %)	103 (59.2)	45 (67.2)	0.255
Hyperlipidemia (n, %)	60 (34.5)	27 (40.3)	0.400
HbA1C (%)	5.8 (5.50-6.50)	5.70 (5.40—6.80)	0.501
Fasting glucose (mg/dl)	104 (96-126.25)	105 (91-125)	0.703
Creatinine (mg/dl)	0.74 (0.65-0.92)	0.79 (0.68-0.97)	0.215
GFR (mL/min/1.73m2)	93 (82-104.25)	92 (78-100)	0.115
LDL-C (mg/dl)	128.28±44.15	121.91±38.40	0.211
Triglyceride (mg/ml)	132(96-188.25)	142 (107-184)	0.428
HDL-C (mg/dl)	46.5 (38-55)	45 (38-57)	0.901
Albumin (g/l)	4.38 (4.16-4.54)	4.4 (4.1-4.60)	0.681
CRP (mg/l)	0.26 (0.16-0.42)	0.33 (0.21-0.45)	0.128
Hemoglobin (g/dL)	13.49±1.60	13.83±.55	0.136
Neutrophil count(10e3/Ul)	4.33 (3.58-5.04)	4.43 (3.58-5.58)	0.333
Platelet count (10e3/Ul)	259.61±61.69	253.53±75.53	0.507
Lymphocyte count (10e3/Ul)	2.42±0.74	2.24±0.77	0.110
Monocyte count (10e3/Ul)	0.56 (0.47-0.70)	0.60 (0.47-0.75)	0.240
MPV (fL)	10.25±0.89	10.61±1.07	**0.009**
ACE /ARB (n, %)	80 (46)	38 (56.7)	0.135
Beta blocker (n, %)	89 (51.1)	33 (49.3)	0.792
Ca channel blocker (n, %)	56 (32.2)	27 (40.3)	0.235
Diuretic (n, %)	57 (32.8)	27 (40.3)	0.271
Statin (n, %)	61 (35.1)	28 (41.8)	0.332
ASA (n, %)	57 (32.9)	29 (43.3)	0.134
Vertebral artery blood flow volume (ml/min)	270 (230-320)	180 (153-200)	**<0.001**
Mean TIMI frame count	21 (19.6-22.3)	27 (21.6-29.3)	**<0.001**
LAD TIMI frame count	22 (20-23)	24 (21-34)	**<0.001**
CX TIMI frame count	21 (18-22.25)	24 (21-26)	**<0.001**
RCA TIMI frame count	21 (19-23)	25 (21-33)	**<0.001**

ACE/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, ASA: Acetyl salicylic acid, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, Cx: Circumflex artery, GFR: Glomerular filtration rate, HDL-C: High density lipoprotein cholesterol, LAD: Left anterior descending artery, LDL-C: Low density lipoprotein cholesterol, MPV: Mean platelet volume, RCA: Right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

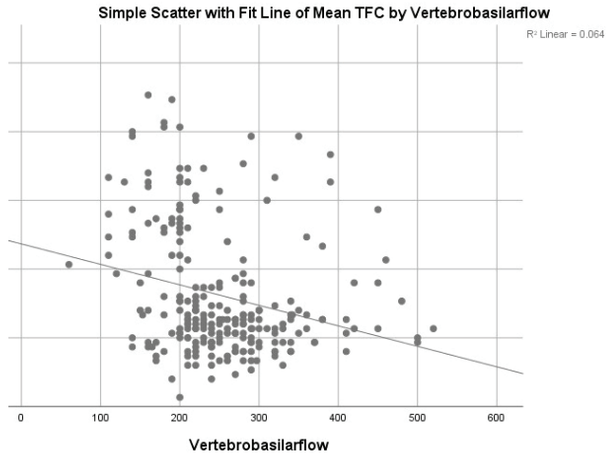

Figure 2 – Correlation of the TIMI frame count with the vertebral artery blood flow volume

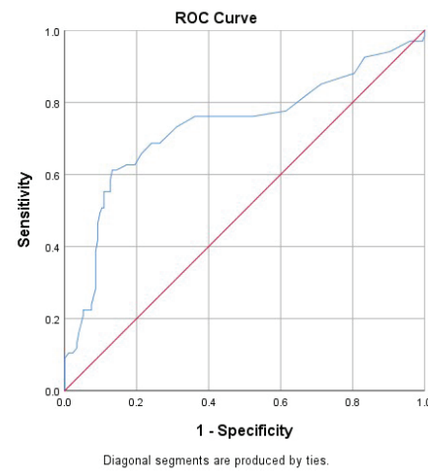

Figure 3 – ROC curve analysis of the TIMI frame count for the prediction of VBI

Table 2 Correlation of vertebral artery blood flow volume with mean TIMI frame count, LAD, Cx and RCA TIMI frame counts.

	r	p
Mean TIMI frame count	-0.278	<0.001
LAD TIMI frame count	-0.250	<0.001
CX TIMI frame count	-0.249	<0.001
RCA TIMI frame count	-0.234	<0.001

Cx: Circumflex artery, LAD: Left anterior descending artery, RCA: Right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Table 3 Univariate logistic regression analysis for the prediction of vertebrobasilar insufficiency.

	p	OR	95% CI
Age	0.054	1.013	0.999-1.064
BMI	0.341	1.023	0.976-1.073
Smoking	0.672	1.130	0.643-1.985
Diabetes mellitus	0.321	0.715	0.359-1.396
HbA1C	0.442	0.998	0.993-1.004
Fasting glucose	0.573	1.000	0.994-1.006
Creatinine	0.599	0.950	0.784-1.150
LDL-C	0.221	0.995	0.987-1.003
Triglyceride	0.465	1.001	0.998-1.004
HDL -C	0.604	1.005	0.985-1.025
Albumin	0.641	1.202	0.555-2.599
CRP	0.954	1.019	0.543-1.911
Hemoglobin	0.137	1.145	0.958-1.368
Neutrophil count	0.114	1.175	0.962-1.434
Platelet count	0.505	0.999	0.994-1.003
Lymphocyte count	0.111	0.731	0.498-1.074
Monocyte count	0.163	3.008	0.641-14.116
MPV	0.010	1.476	1.096-1.990
Mean TIMI frame count	<0.001	1.069	1.046-1.094
LAD TIMI frame count	<0.001	1.138	1.083-1.195
CX TIMI frame count	<0.001	1.138	1.071-1.209
RCA TIMI frame count	<0.001	1.142	1.085-1.201

ACE/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, ASA: Acetyl salicylic acid, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, Cx: Circumflex artery, GFR: Glomerular filtration rate, HDL-C: High density lipoprotein cholesterol, LAD: Left anterior descending artery, LDL-C: Low density lipoprotein cholesterol, MPV: Mean platelet volume, RCA: Right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Table 4 Multivariate logistic regression analysis for the prediction of vertebrobasilar insufficiency.

	p	OR	95% CI
Mean TIMI frame count	<0.001	1.066	1.043-1.091
MPV	0.123	1.303	0.931-1.825

MPV: Mean platelet volume, TIMI: Thrombolysis in Myocardial Infarction.

Our results revealed that 148 (84.6%) patients who did not have CSFP also did not have VBI, whereas 40 (60.6%) patients who had CSFP also had VBI. The mean TIMI frame count and LAD, Cx, and RCA TIMI frame counts were negatively correlated with the vertebral artery blood flow volume ($p<0.001$ for all). Table 2 and Figure 2 show the correlations among the variables. A mean TIMI frame count of 24.5 predicted VBI, with a sensitivity and specificity of 61.2% and 86.8%, respectively (area under the curve: 0.732, 95% confidence interval 65.2%-81.1%, $p<0.001$) (Figure 3).

The results of univariate logistic regression analysis revealed that the mean platelet volume and mean TIMI frame count were absolute predictors of VBI. The only predictor of VBI was the mean TIMI frame count (OR: 1.066, 95% confidence interval: 1.043–1.091, $P<0.001$). (Tables 3 and 4).

Discussion

Our results revealed that CSFP was associated with decreased vertebrobasilar blood flow volume and was an independent predictor of VBI, suggesting a common pathophysiological mechanism underlying both disorders.

Posterior circulation remains an important source of ischemic stroke, accounting for approximately 20% of cases [10]. Compared with patients who do not have vertebrobasilar occlusion, patients who have a transient ischemic attack or stroke and who have verebrobasilar occlusion are at substantial risk of recurrent stroke [11]. One study showed that a stenosis of more than 50% of the vertebral or basilar arteries was linked to a greater risk of stroke than a similar occlusion of the carotid arteries [12]. Subjects with symptomatic vertebrobasilar disease have one-year and five-year stroke-free survival rates of 67% and 48%, respectively [13]. As such, vertebrobasilar disease is a major cause of disability. Similarly, subjects with VBI tend to have high long-term morbidity and mortality, and because VBI is associated with nonspecific symptoms, it is usually an underdiagnosed condition [14].

Several pathophysiological mechanisms have been proposed for the development of CSFP. The coronary endothelium acts as a barrier between vascular tissue and plasma; in addition to vasodilation and contraction, it plays several important roles in regulating vascular tone, homeostasis and cellular adhesion [15]. In patients with CSFP, endothelium-dependent flow-mediated dilation is impaired, suggesting a role for endothelial dysfunction in the development of CSFP [16]. Vascular endothelial cells help maintain vascular tone by secreting vasoactive substances [17]. Nitric oxide, produced by endothelial nitric oxide synthase, is a potent vasodilator that regulates platelet activity, leukocyte adhesion and angiogenesis [18]. Studies have shown that patients with CSFP have significantly lower levels of plasma nitric oxide synthase, suggesting a link between endothelial dysfunction and CSFP [19, 20]. Inflammatory cytokines such as interleukins, tumor necrosis factor-α, C-reactive protein, and inflammatory biomarkers such as platelet-to-lymphocyte ratios and fibrinogen-to-albumin ratios were found to be increased in CSFP patients, suggesting that inflammation is involved in the pathogenesis of CSFP [21, 22]. These patients have elevated levels of inflammatory markers and abnormal hemorheologic properties, predisposing them to CSFP [23–26]. Beltrame et al. reported that CSFP is associated with increased coronary microvascular tone, confirming the role of microvascular abnormalities in this group of patients [27]. Patients with CSFP had coronary arteries with a normal appearance on coronary angiographic examination, but histopathologic examination of coronary arteries revealed small vessel abnormalities, including medial hypertrophy, endothelial degeneration and capillary damage [28]. In addition, functional abnormalities such as increased resistance of small coronary vessels have been reported [27, 29]. A combination of these mechanisms could lead to reduced myocardial blood flow and anginal symptoms. Several studies have demonstrated subclinical atherosclerotic involvement of the coronary arteries in this group of patients. Intravascular ultrasound of the coronary arteries revealed both epicardial atherosclerotic involvement and microvascular abnormalities [30, 31].

The evaluation of vertebral blood flow/velocity via Doppler sonography is a widely available and commonly used technique that provides important information regarding the hemodynamics of the vertebral arteries. It allows physicians to perform initial and serial assessments of the vertebral arteries. Acar et al. investigated Doppler vertebral artery blood flow volume to diagnose VBI. In their study, patients were divided

into three groups according to vertebral artery blood flow—severely attenuated flow volume, moderately attenuated flow volume, and normal flow volume—and vertebral artery blood flow volume measurements were more valuable than velocity measurements for the diagnosis of VBI [32]. In the present study, we evaluated vertebral blood flow via Doppler sonography and reported that TIMI frame counts were negatively correlated with vertebral artery blood flow volume. Our study highlights a common mechanism that affects more than just one vascular bed. Patients should therefore be followed up regularly, their risk factors should be treated, and emphasis should be placed on lifestyle changes.

Conclusion

Our results showed that patients who had CSFP had a greater incidence of VBI and that CSFP had good specificity for predicting VBI. Moreover, it was an absolute predictor of VBI. The TIMI frame count and vertebral artery blood flow volume were negatively correlated with each other. These findings suggest a common pathophysiological mechanism underlying both clinical conditions. Our results also revealed that the presence of CSFP indicates a more generalized phenomenon.

Limitations: We enrolled patients from a single center, and our study population was small. Patients were not followed longitudinally.

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Coexistence of Unruptured Twin Tubal Ectopic Pregnancy with Tubo-Ovarian Abscess in the Same Adnexa: a Case Report and Literature Review

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Abstract

Ectopic pregnancy is the implantation of a gestational sac outside of uterine cavity. Majority of cases occur in the fallopian tubes. It has remained one of the leading causes of first trimester cause of maternal mortality. Incidence has increased with increase in sexually transmitted diseases and assisted conception and improved earlier diagnosis while mortality has reduced due to improved earlier diagnosis with more conservative and less invasive treatment modalities. Tubo-ovarian abscess (TOA), an ascending polymicrobial infection of the upper genital tract in females usually presents with symptoms such as lower abdominal pain, bleeding from the vagina and fever, which sometimes presents a diagnostic dilemma between TOA and ectopic pregnancy. Both disease conditions are potentially life threatening. We present a case of a 33-year-old woman with co-existing TOA and unruptured ectopic pregnancy.

Keywords: Tubal ectopic pregnancy, tubo-ovarian abscess, salpingectomy.

Introduction

Ectopic pregnancy is the implantation of the gestational sac outside of the endometrial cavity [1, 2]. It occurs in 1.3 to 2.4% of pregnancies in the reproductive age group [1, 3] . It has remained the leading cause of first trimester maternal morbidity and mortality [1–4]. Majority of the ectopic gestations (95%) are located in the fallopian tube and the rest found at other sites like the; ovary, cervix, and intra-abdominal region [1–4]. The risk is increased with a background history of sexually transmitted diseases, pelvic inflammatory disease, previous pelvic surgery especially tubal surgery, assisted conception, history of infertility, smoking and in utero exposure to Diethylstilbesterol [4, 5]. Incidence is increased amongst pregnancies occurring with the use of intra-uterine device and progesterone only contraceptive use. [4]. Amenorrhoea, lower abdominal pain and vaginal bleeding are the classic symptoms triad of ectopic pregnancy, and acute abdominal symptoms and hemodynamic instability can be seen with its rupture [2, 4]. Presentation as an infected ectopic pregnancy is rare and is usually the result of a tubal abortion or a ruptured ectopic pregnancy with a subclinical self-limiting hemodynamic insult and a superimposed infection of the conceptus. [6]. Infected ectopic pregnancy may be seen as a variant of chronic ectopic pregnancy where the trophoblastic tissue gradually invades through the implantation site leading to repeated rupture at the site and continued sub-clinical bleeding over time forming a haematocele and appear as a pelvic mass or abscess [2, 6]. The pathological process is usually that of a large, infected, walled-off hematoma around the products of conception in the distal half of the fallopian tube and may involve adjacent organs [6]. Presentation as a tubo-ovarian abscess is most often unilateral [6]. Tuba-ovarian abscess by tubal distortion can be a precursor and consequence of ectopic pregnancy and may rarely be found together.

TOA most times occur as a complication of poorly treated or untreated pelvic inflammatory disease (PID). It is a polymicrobial infection of aerobic and anaerobic bacteria seen frequently in the reproductive years [7]. Poorly treated tubo-ovarian abscess can lead

to ectopic pregnancy, infertility, chronic pelvic pain, ovarian vein thrombosis, and pelvic thrombophlebitis. [7] Delayed intervention could result in rupture, peritonitis, sepsis and death [7]. Medical treatment for tubo-ovarian abscess gives good outcome in 75% of patients and the rest needing surgical intervention [7].

Co-existence of tubal ectopic pregnancy with tubo-ovarian abscess can sometimes present a diagnostic challenge as both may have similar symptoms. Surgical treatment (Laparoscopy or Laparotomy) is usually preferred treatment choice.

Case

Patient was a 33-year-old Para 4 (4 alive) woman who presented with lower abdominal pains of one week duration. She presented to our facility three months ago during which a diagnosis of Pelvic inflammatory disease was made. She was counseled to bring her husband for testing and treatment. However, she was lost to follow up. She also stopped her prescribed oral antibiotics as soon as her symptoms subsided. Her last menstrual period was 6 weeks ago.

On presentation, her vital signs were Heart rate 100 bpm, SO2 of 98%, BP 100/60mmHg. Abdominal examination revealed tenderness on the left iliac fossa. Speculum examination showed closed cervical os with muco-purulent discharge in the posterior fornix. Packed cell volume was 30%, white cell count was 24, 000 X 106 with predominant of neutrophils, blood borne viruses were negative, Random blood sugar was 122mg/dl, and Serum B-HCG was positive. A pelvic ultrasound scan done revealed an empty uterus, 2 gestational sacs with fetal poles without cardiac activities at the left adnexa and a multilocular complex left adnexal mass of 7.4 cm lateral to the gestational sacs. A diagnosis of twin tubal ectopic pregnancy with suspicion of co-existing tubo-ovarian abscess was made. She was counseled on treatment options (laparoscopy, laparotomy). However, she opted for laparotomy on account of financial constraint. She subsequently had Laparotomy (using Maylard transverse incision)with salpingectomy and drainage of pelvic abscess.

Intra operative findings were 500mls of sero-purulent ascites, moderate adhesions of uterus to bladder anteriorly, and uterus to bowel posteriorly, estimated blood loss was 950mls. Sample was taken for aerobic and anaerobic culture and tubal specimen was sent for histology. The right fallopian tube was grossly healthy. She was transfused with 2 units of blood post-operatively on account of post of anaemia. Her post op recovery was uneventful, and she was discharged on third post operative day.

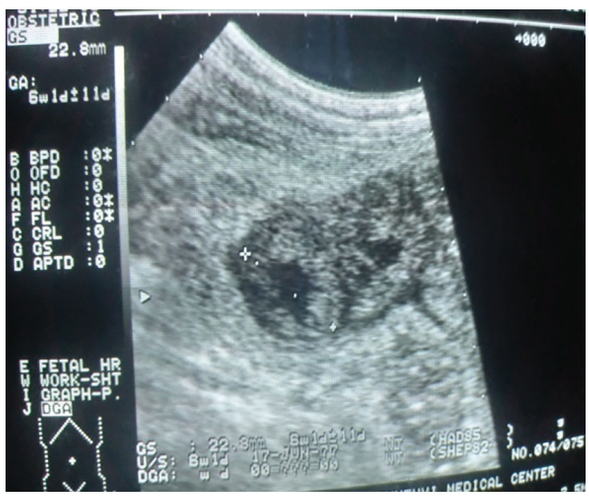

Figure 1 – Pelvic ultrasound scan demonstrating two extra-uterine gestational sacs with fetal poles

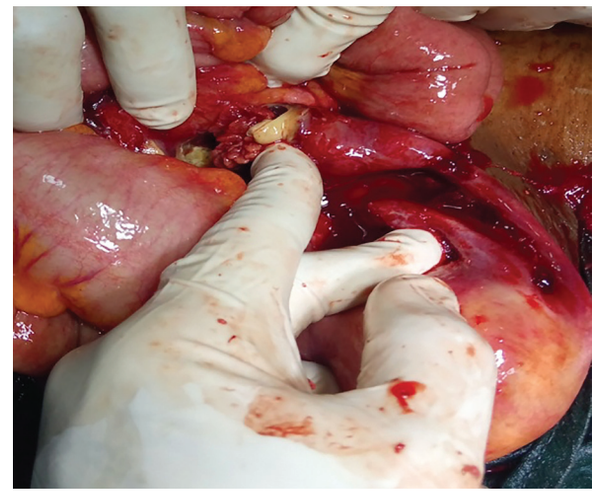

Figure 2 – Intra-operative findings of pus in the left adnexa with pustular exudate from the left fimbrial end respectively

Discussion

Ectopic pregnancy as the most important cause of first trimester maternal morbidity and mortality has increased in recent years with increase of sexually transmitted diseases and widespread access to assisted reproductive techniques [4, 7, 8]. Fatality from ectopic pregnancy has also declined despite the rise in incidence due to early presentation, improved diagnosis and better treatment options especially in the developed world [4].

Tubo-ovarian abscess is usually seen in the reproductive period and mostly polymicrobial agents being responsible for the infective process [7, 8]. Tubo-ovarian abscess is usually seen as inflammatory masses involving the fallopian tubes and is highly associated with the ovaries and other pelvic structures [1]. The aetiology of the co-existence of ectopic pregnancy with tubo-ovarian abscess is not clear, however; ascending infection being the likely route following documented cases seen in the presence of; IUD, previous PID and curettage just prior to the inflammatory process [6]. Direct or contiguous spread could be responsible for cases after a ruptured appendicitis with peritonitis. [6] These may lead to infection of the walled-off hematoma around the conceptus [6]. Pelvic inflammation is a risk factor for ectopic pregnancy altering tubal motility, a history which was present in the case presented. The patient was screened for diabetes and Human immunodeficiency virus both of which are common causes of reduced immunity and favourable for abscess formation. Malnutrition and anaemia could possibly predispose the patient to abscess following ascending pelvic infection for one in a polygamous sexual relationship.

Early diagnosis and intervention correlates with a more favourable outcome for both ectopic pregnancy and tubo-ovarian abscess individually and same should apply when both

co-exist [8]. Treatment delay apart from posing a fertility risk, more importantly a rupture can be fatal [9].

Amenorrhoea, lower abdominal pain with or without vaginal bleeding are common alongside other non specific symptoms [2, 3]. Patient may be septic in acute cases with acute or low grade pyrexia [6].

Advancement in ultrasonography has led to earlier, easier and increased diagnosis with reduced mortality [2, 3].

Inflammatory markers such as neutrophiliaand elevated CRP are common in the presence of abscess. Anaemia may complicate sepsis or tubal rupture [2].

Beta- Human chorionic gonadotropin may be positive or weakly positive in protracted or chronic cases as a result of inactive or avital trophoblast tissues which may create a

diagnostic challenge [2, 6]. Ultrasound scan usually gives the differentials of tubo- ovarian abscess/chronic inflammatory mass [2]. Other sonographic differentials include ovarian dermoid cyst, haemorrhagic cyst and endometrioma [6]. Transvaginal Ultrasonography may easily demonstrate a gestational sac with yolk sac in the affected adnexa [1]. Magnetic resonance imaging (MRI) scans can be helpful as it may demonstrate features such as presence of a haemoperitoneum associated with haematosalpinx and prominent enhancement of the tubal walls with the concurrent presence of a pelvic mass [2]. This may not be readily available and accessible in most places in our environment.

Ectopic pregnancy can also be diagnosed retrospectively on histology by presence of chorionic villi after surgical treatment for tubo-ovarian abscess [2, 6].

Differential diagnoses include other unilateral pelvic masses common with young women which may look both clinically and sonographically like a pelvic or tubo- ovarian abscess such as IUD-associated tubo-ovaran abscess, infected ovarian cysts, haemorrhagic ovarian cysts, endometrioma, cystic teratoma complicated by torsion or rupture, periappendicular abscess with low-lying caecum, or an inflammatory mass of Crohn's disease and dermoid [6, 8].

Laparoscopy is accepted as the gold standard in the diagnosis and treatment of ectopic pregnancy and tubo-ovarian abscess where available with the right manpower in a hemodynamically stable patient [2, 4]. Laparotomy was performed as that was what could be offered and her anaemic state made referral for laparoscopy a concern. The decision for salpingectomy or salpingostomy in tubal ectopic surgery depends on the age of the patient and the desire for fertility and the status of the contralateral tube [1, 4]. Tubo-ovarian abscess inflicts further tubal damage than would have ordinarily been caused by an ectopic pregnancy. In our case, the affected tube was highly hydropic with pustular discharge from the tube. The patient did not desire further fertility with a healthy-looking contralateral tube, hence a salpingectomy of the affected was done.

Surgical treatment is the treatment of choice preferably laparoscopically where available [2]. It is often difficult to perform conservative surgery due to extensive damage of the tube and the severity of pain symptoms [2]. Reduced amount of active chorionic villi and minimal or absent trophoblast activity may explain poor outcomes with methotrexate [2, 10]. It is important to state that this very rare subset of ectopic pregnancy also poses a significant diagnostic and treatment dilemma especially in developing countries with paucity of trained gynaecologists [11].

In conclusion, early diagnosis of co-existing ectopic pregnancy with tubo-ovarian abscess is necessary to allow for early and appropriate intervention which could help limit damage and prevent even more fatal complications. This case report also highlights the importance of considering alternative diagnoses in any reproductive age woman presenting with similar symptoms.

Clinical implications of this case report

Co-existence of tubal ectopic pregnancy and TOA can present with a myriad of non-specific signs and similar symptoms therefore posing a very serious diagnostic challenge to the gynaecologist. Multimodality gynaecological imaging such as 3-dimensional transvaginal ultrasonography, pelvic computed tomography (CT) scan and magnetic resonance imaging (MRI) with high index of suspicion will help mitigate the maternal morbidity and mortality attributed to this clinical entity.

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