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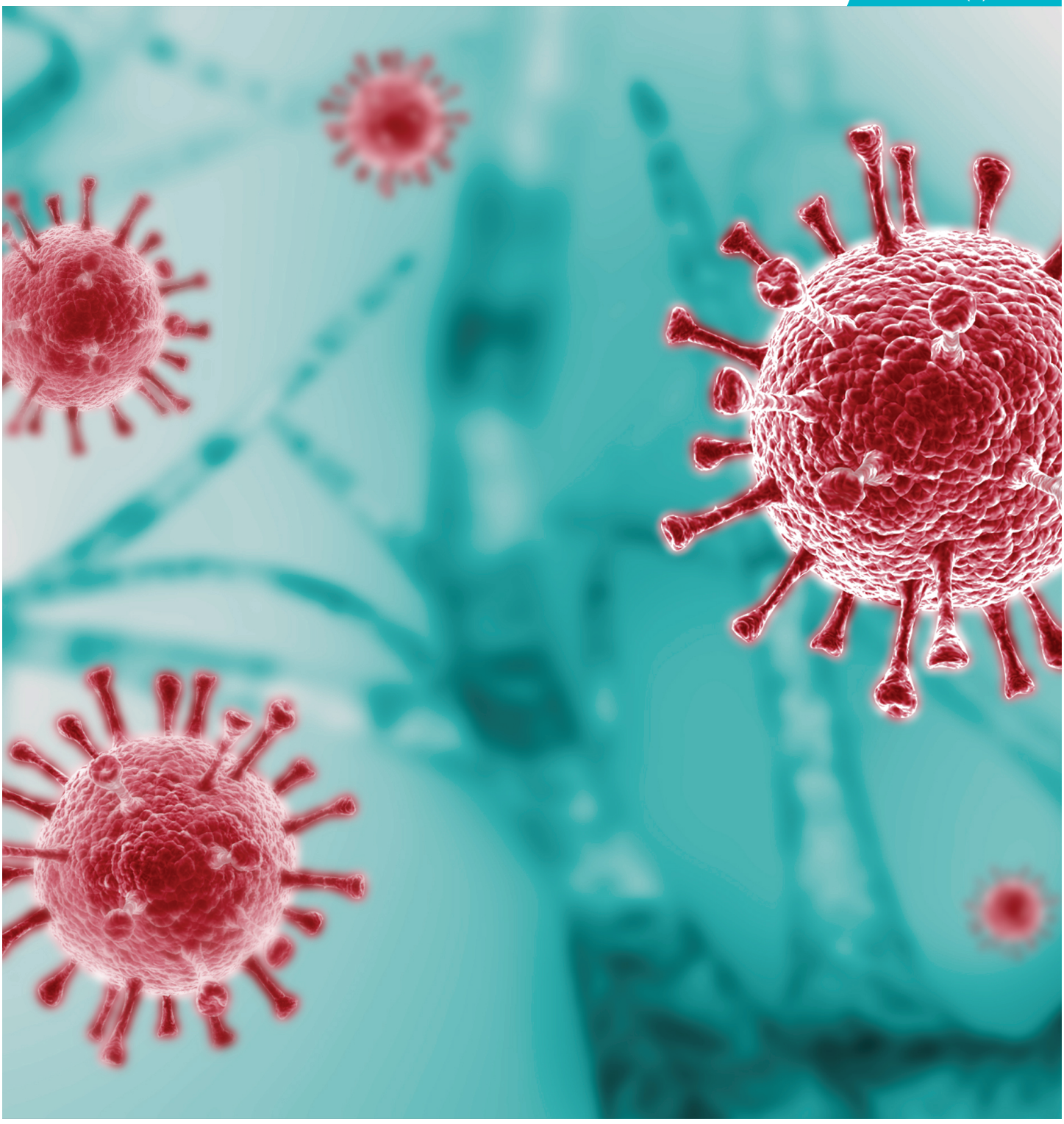

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Kazakhstan CTO Club's recommended guidelines for interventional therapy for coronary chronic total occlusion

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Abstract

Chronic total occlusion (CTO) disease refers to obstructive coronary artery disease, which is the degree of direct blood flow of the blood flow TIMI 0 degree of occlusion time 3 months, if there are already well-developed collaterals or bridge collaterals, the distance from the occlusion of the blood vessel TIMI blood flow > 0 degree is still considered a total occlusion disease. Previous studies have shown that 20% of patients with coronary heart disease have experienced CTO lesion from at least one vessel, Percutaneous Coronary Intervention (PCI) surgery is called the "last fortress" in the field of coronary intervention because of the low success rate and high complications. Therefore, based on the integration of the clinical experience of our country and the analysis of relevant information and progress in research in this area, Chronic Total Occlusion Club Qazaq (Chronic Total Occlusion Club Qazaq, CTOCQ) developed a proposed method of interventional treatment of Coronary chronic total occlusion in Kazakhstan for reference to interventional doctors.

Key words: interventional therapy, chronic, total occlusion, guideline

Introduction

Chronic total occlusion (CTO) disease refers to obstructive coronary artery disease, which is the degree of direct blood flow of the blood flow TIMI 0 degree of occlusion time 3 months, if there are already well-developed collaterals or bridge collaterals, the distance from the occlusion of the blood vessel TIMI blood flow> 0 degree is still considered a total occlusion disease [1-2]. Previous studies have shown that 20% of patients with coronary heart disease have experienced CTO lesion from at least one vessel [3], Percutaneous Coronary Intervention (PCI) surgery is called the "last fortress" in the field of coronary intervention because of the low success rate and high complications [2]. Clinical data indicate that the success of CTO lesion revascularization effectively facilitates myocardial ischemia and angina pectoris [4-6], improves left ventricular function [7,8], reduces the need for a bridge in the coronary artery [9,10], and improves clinical recovery [11-15]. According to the results of available clinical trials [16,17], revascularization therapy should be considered if patients still have symptoms such as heart failure due to myocardial ischemia and blockage of blood vessels. If the patient does not have the appropriate symptoms, a non-invasive examination is recommended (for example, a strength test, a rest/stress echocardiography, a radionuclide study of the rest/stress heart, and so on.). Medications can be used for CTO lesion that has no evidence of myocardial viability or dominates the myocardium in small quantities.

CTO-PCI does not have a high success rate in the beginning, 50%-70% [9,10,18,19]. But with the development of modern equipment and technology [20-22], the profitability of CTO-PCI in many centers around the world has exceeded 80% [23-25] some centers can reach about 90%. The level of development of regional interventions in our country is uneven, and the popularity of new types of equipment is low. Objective factors to a certain extent hinder the process of CTO-PCI treatment standards in our country. Therefore, based on the integration of the clinical experience of our country and the analysis of relevant information and progress in research in this area, Chronic Total Occlusion Club Qazaq (Chronic Total Occlusion Club Qazaq, CTOCQ) developed a proposed method of interventional treatment of Coronary chronic total occlusion in Kazakhstan for reference to interventional doctors.

CTO-PCI technology, strategy overview and recommended way

Detailed assessment of CTO-PCI lesion visualization (Imagine Science)

Thorough and repeated vision of coronary angiography, which is the basis of interventional treatment of CTO lesions. Most CTO lesions require polygonal bilateral coronary angiography before interventional treatment. In case of CTO lesions with well-developed spontaneous collateral vessels during interventional treatment, it is recommended to perform bilateral coronary angiography or perform super selective contrast with independently developed collateral vessels in order to reduce lesion to the target blood vessels caused by the inserted contrast. Coronary CT angiography (CCTA) is recommended before repeating interventional treatment for CTO lesions that previously failed attempts or have complex anatomical structures (for example, severe curvature, abnormal hole origin, and total occlusion of the primary part).

The assessment of the visualization of the CTO lesion (Imagine Science) includes the anatomy of the nearest end of the CTO lesion (morphology of the displacement site, whether the occlusal end has large branched blood vessels), the vascular part of the CTO lesion (calcification, curvature, length of the occlusal segment) [26] and the far end of the CTO lesion (the form of a fibrous valve, does the far end of the occlusion have large branched blood vessels, or does the far end of the occlusion end in a bifurcated lesion, diffuse lesions in the occlusal segment and segment are there at the end of blood vessels in occlusal segment?). In addition, it is necessary to carefully assess the presence of collateral blood vessels that have an opposite entrance. attention should be paid to the way of development of collateral vessels of the opposite direction, the diameter of their width, the degree of curvature, the angle between the collateral blood vessels and the blood vessels of the donor /acceptor (host), the distance between the collateral blood vessels and the far end of the occlusion after entering the blood vessels of the acceptor, etc. [27-29] if collaterally donor blood vessels have lesion that can affect blood flow or acute occlusion, the lesion must first be treated before starting retrograde direction interventional treatment.

Strategic planning of CTO-PCI interventional therapy

Initial statement of the CTO-PCI strategy

(1) The initial strategy for defeating a CTO with a truncated trunk involves entering the standing side (antegrade). If there is an unspecified anatomical structure or an indistinct lesion of the SRT, if possible, intravascular ultrasound (intravascular ultrasound IVUS) interventional therapy can be performed.

(2) Antegrade dissection re-entry technique (ADR) [30-34] strategy: entry in the former antegrade direction in case of failure of interventional treatments, in poor condition of the branched (collateral) vessel or in the former retrograde direction direction (retrograde) interventional treatments were stepless and are used in occlusion in the occlusive segment and occlusive segment without diffuse lesions of blood vessels and in the landing zone , and the length of the occlusal segment is more than 20 mm

(3) For CTO lesions that are inconvenient for direct interventional treatment, direct retrograde direction interventional therapy can be used if there are effective collateral vessels in the opposite direction.

Strategy regulation in the CTO-PCI process

(1) The key to adjusting the strategy in the CTO-PCI process is to change the strategy in a timely manner.

(2) If the direct guide wire(wire) cannot pass through the occlusion section, ADR technology or parallel guide wire technology can be considered. To improve the success rate of parallel guide wire technology, KDLC (Kaneka Corporation) or SASUKE (Asahi INTECC co., LTD.) a two-Lumen microcatheter can be considered as a parallel guide wire technology driven by a double-lumen microcatheter.

(3) However, if the distant blood vessels in the occlusal segment have significant diffusion lesion, the probability of success of parallel conductor technology and ADR technology is often low. In the presence of lateral blood vessels that are effective for use, direct retrograde direction interventional therapy can be used.

(4) Antegrade and retrograde directions combination technique (two-way preparation): It is difficult to succeed in complex CTO lesions, antegrade or retrograde directions strategies. After the entrance in the antegrade direction failed, the technique in the opposite direction should be picked up earlier or interventional treatment in the opposite direction should be carried out immediately [35]. In some cases, ADR technology can be used together.

Preoperative preparation of CTO-PCI

The method of interventional therapy should be chosen based on factors such as the underlying condition of the patient, the habits of the surgeon, the methods and equipment usedn [36]. There is strong active support (backup) based on compliance prerequisites It is recommended to use the assessment catheter as much as possible. EBU (MEDTRONIC, INC) XB (CORDIS Corporation) AMPLATZ catheters and other guide catheters, it is recommended to use AMPLATZ XB RCA (CORDIS Corporation) and other guide catheters for the right coronary artery If you plan to implement IVUS guidance in real time, it is advisable to use at least 7F catheters for routing; if you plan to combine KDLC double lumen microcatheters and IVUS catheters, it is worth using 8F-guide catheters; If you cannot use 8F guide catheters, but cannot use double lumen microcatheters for interventional treatment with IVUS, you can choose SASUKE double lumen microcatheters or use the Ping-pang guide catheter method (ping-pang guide catheter technique); When operating ADR equipment, it is recommended to use 7 F / 8 F guide catheters. A guide catheter with lateral openings helps to reduce the probability of coronary artery lesion caused by coronary artery ischemia and contrast injection.

To prevent catheter thrombosis, regular use of conventional heparin for anticoagulation during the CTO-PCI process and constant monitoring during surgery (activated clotting time-ACT) is recommended. It is recommended to monitor once every 30-45 minutes to maintain the ACT at 250-350 °C

CTO-PCI technology

Antegrade direction CTO-PCI technology

(1) Selection and replacement of guide wires in the antegrade direction (Table 1): for the defeat of CTO with conoid tubercles, it is recommended to start with the design of a conoid head with a low and medium degree of polymer coating. If the primary guide wire cannot pass occlusal lesion, it is recommended to update the middle penetrating guide wire. If the aforementioned guide wire still cannot pass through the

Table 1 Frequently used guide wire by CTO-PCI

category	name	polymer coating	diameter of the cone end (in)	End stiffness (g)	country-manufacturer
degree of puncture low	Fielder XT	Y	0.009	0.8	Asahi Intecc
	Fielder XT-R	Y	0.010	0.6	Asahi Intecc
	Fielder XT-A	Y	0.010	1.0	Asahi Intecc
	Pilot 50	Y	N	1.5	Abbott Vascular
	Gaia First	N	0.010	1.7	Asahi Intecc
	Cross-it 100 XT	N	0.010	2.0	Abbott Vascular
degree of puncture medium	Pilot 150	Y	N	2.7	Abbott Vascular
	Pilot 200	Y	N	4.1	Abbott Vascular
	Miracle 3	N	N	3.0	Asahi Intecc
	Ultimate Bros 3	N	N	3.0	Asahi Intecc
	Gaia Second	N	0.011	3.5	Asahi Intecc
	Cross-it 200	N	0.011	3.0	Abbott Vascular
degree of puncture penetration	Conquest Pro	N	0.009	9.0	Asahi Intecc
	Conquest Pro 12	N	0.009	12.0	Asahi Intecc
	Gaia Third	N	0.012	4.5	Asahi Intecc
	Progress 200T	N	0.009	13.0	Abbott Vascular
	Miracle 12	N	N	12.0	Asahi Intecc
	Conquest Pro 8-20	N	0.008	20.0	Asahi Intecc

Note: CTO, chronic total occlusion; PCI, Percutaneous Coronary Intervention; l in = 2,54 см

occlusive disease, it can be upgraded to a guide wire that enters upwards. In case of CTO lesion, in which the eye is not clearly visible, for example, the presence of vessels of the corresponding branch at the proximal end of occlusion, IVUS visualization is recommended for the direction of proximal puncture of the fibrous cover. A medium penetration guide wire can be used first, if it fails, it is recommended to use a high penetration guide wire. After the conductive wire with high permeability passes through the proximal fibrous coating, if the occlusion segment is long or the way is unclear, it can be replaced with a medium penetrating guide wire (step Down), in some cases, when this conductive wire enters the distal fibrous coating, it is necessary to use a high-penetrating guide wire (step up) with good processing ability. Gaia series (ASAHI INTECC CO. LTD.) for solid calcifications, twists and occlusive lesions with a long segment. Use the guide wire with caution.

(2) Antegrade direction guide wire technique: When intervening in the antegrade direction, if the occlusal segment is short, it is recommended to first use the technique of moving the guide wire up its own ladder. If the occlusal segment is long or the technique of replacing the guide wire failed, in addition, the distal blood vessels of the occlusal segment do not have diffuse disease, and the landing zone does not contain large branched vessels, ADR technology [based on Crossboss (Boston Scientific Corporation) Stingray (Boston Scientific Corporation)balloon [30-31] or technology of entry from the false lumen based on the guide wire into the true lumen [32-34] should be considered.. In some cases, within the framework of IVUS, a guide wire can be inserted from a false lumen into a true one [37]. If you cannot perform ADR technology, try using parallel guide wire technology or retrograde guide wire technology. when the antegrade pointing wiring technique fails, it is recommended to start the retrograde-direction intervention therapy as early as possible, if there are available branched vessels (Collateral circulation).

(3) The way to solve problems, when the guide wire prevents the passage of the equipment (instrument) through the lesion, the CTO / balloon cannot rise: if the equipment is difficult to deliver forward, after confirming that the guide wire is in the true lumen of the remote vessel, the technology of deep intake of the guide catheter, Balloon anchoring technology (when there is a large branch nearby), Buddy wire guide technology [38] Baby and mother catheter technology,GUIDEZILLA catheter technology (Boston Scientific Corporation)The TORNUS catheter (ASAHI INTECC Co., LTD.) [39] To expand occlusal lesion, it is necessary to use a thin balloon with a width of 1 mm and a length of 20 mm, an excimer laser, coronary drilling (Rotablator) and other methods. If it is not possible to expand the balloon, you can use the technology of double balloon - staggered cutting guide wire (double balloon-staggered cutting guide wire), two guide wire technology of alternating with one balloon, Tornus catheter, excimer laser, Rotablator and other methods.

Retrograde direction CTO-PCI technology

(1) Selection and manipulation of retrograde direction guide wire: selection of Collateral circulation. In retrograde direction interventional therapy, septal vessels are usually slightly analyzed, but well-developed epicardial collateral vessels can also be used with caution. Some patients after coronary artery shunt surgery may use a vessel shunt. ②selection of the guide wire passing through the collateral vessels (Table 2), Usually, the wire is chosen soft, well-sensitive to the hand when inserted, a guide wire, convenient for passing through the curved part. Representative guide wire - Sion (ASAHI INTECC Co., LTD.). Fielder X TR (ASAHI INTECC CO., LTD.) should be used if the collateral vessels (Collateral circulation) are strongly curved and the Sion guide wire cannot pass and if the internal lumen of the blood vessel is thin. Try using a guide wire, but the surgeon should be careful, it is advisable to be careful not to get into an invisible branch. If the circle of collateral vessels is large, Sion Black (ASAHI INTECC CO., LTD.) guide wire can be used. For very strongly curved collateral vessels (collateral vessels such as fast noodles), SUOH 03 (ASAHI INTECC CO., LTD.) guide wire is recommended. After penetration into the lateral Vessel, the shape of the guide wire end should be as short as possible, usually less than 1 mm or 1 mm, with an angle from 70° to 90°. The main method is to conduct a guide wire from the collateral vessel by twisting. do not press hard so as not to lesion the collateral vessel. Some methods of surfing from the Septal collateral vessel [40] can be carried out using a guide wire, but cannot be applied to epicardial collateral vessels. In order not to lesion the collateral vessel, the surgeon should insert a guide wire against the background of highly intelligent angiography.

Table 2 Frequently used guide wire by CTO-PCI

Anatomical features	Intermediate branches	Collateral vessels of the epicardium,
continuous curving	Sion SUOH 03 Fielder XT-R	Sion SUON 03 Fielder XT-R(Small blood vessels) Sion black(Big vessels)
Blood vesssel a branch from a crooked place,	Sion SUON 03 Fielder XT-R(Small blood vessels) Sion black(Big vessels)	SUON 03 Sion Fielder XT-R(Small blood vessels) Sion black(Big vessels)
sharp angle,	SUON 03 Sion Sion black	SUON 03 Sion Sion black
invisible collateral channels	Sion Sion black Fielder XT-R	Avoid actions

Before performing a superselective angiography, the surgeon should try to pump blood from the microcatheter so as not to lesion the guaranteed vessels. ③restoration of collateral vessel lesion. Most of the septal collateral vessel is damaged without serious consequences, requires only a thorough examination. In some patients, after lesion to septic vessels, a large hematoma or perforation occurs, which can lead to hemodynamic instability. Regular, embolization and symptomatic treatment should be carried out on time

When the collateral vessels of the epicardium are damaged, this often leads to tamponade of the heart. The surgeon must actively fight it and carry out embolization on time. If the CTO lesion is opened, the surgeon must not only embolize the donor collateral vessel, but also embolize the target CTO in the opened vessel. If some collateral vessel is damaged, the microcatheter can be stopped by negative pressure, prolonged suction back. Selection of guide wires after passing the collateral vessel. In accordance with the morphology of the distal fibrous valve, which is indicated by super selective angiography, it is recommended to choose different guide wires. If the cover of the distal fiber of the CTO lesion has a conical shape, it is preferable to use a guide wire with low or medium penetration; if there is no end at the end of the distal fibrous cap or the guide wire specified above cannot pass through the distal fibrous cap, it is recommended to replace the guide wire that enters the medium/high.

(2) Selection of microcatheter: Corsair (ASAHI INTECC CO, LTD.) Finecross (Terumo corporation) and etc. choose a microcatheter with a length of 150 cm, in some cases, a 90 cm long guide catheter is required if the developed interval of the collateral vessel is at a great distance. If the Corsair microcatheter cannot pass through the collaterals, you can use the Finecross microcatheter; you can replace the new Corsair microcatheter; Use the Caravel 150 cm microcatheter (ASAHI INTECC CO., LTD.) or Corsair Pro microcatheters (ASAHI INTECC CO., LTD.); balloon attachment technology; Combined use of Guidezilla catheters, etc.; expansion of the septal collateral vessel with a small balloon under low pressure [1,0-1,25 мм, 2-4 атм (1 атм = 101,325 кПа)], but the collateral vessel of the epicardium cannot be used; Use a Threader Catheter (Boston Scientific Corporation); In some cases, you can first use the Corsair 135 cm microcatheter, and then switch to the Corsair 150 cm catheter. If none of the above methods gives results, it is recommended to analyze another collateral vessel in time or continue in the antegrade direction, standing on the retrograde direction of the guide wire.

(3) Commonly used retrograde guide wire technology:the technology of the guide wire in the retrograde direction mainly includes the technology of conducting wiring in the retrograde, the technology of docking the wire in the retrograde, antegrade directions, the technology of tracking the path through the inner curtain (controlled antegrade and retrograde directions subintimal tracking, CART) with controlling of the guide wire in the retrograde and antegrade directions [41], retrograde direction CART technology. the technology of guide wiring in the retrograde, the technology of connecting guide wiring in the retrograde and antegrade directions are mainly suitable for cases when the length of the damaged part of the CTO is shorter. In case of failure, it is recommended to use retrograde direction CART technology as soon as possible. If it is expected that the distance between the damaged parts of the CTO will be long, curved, the anatomy of the damaged part will be difficult, the chances of success of the guide wire wiring technology in the retrograde, wire docking techniques in the opposite direction will be low. To increase the efficiency and success of the operation, it is recommended to perform the retrograde direction CART technology as soon as possible. With curved, calcified injuries, the usual way of working with wire can puncture blood vessels, if necessary, Knuckle technology can be used. If retrograde direction CART technology fails, consider retrograde direction CART technology within IVUS [42].

(4) The output of the guide wire outside the bode frame : Currently, a 330 cm Rg3 guide wire is recommended for output outside the body frame (ASAHI INTECC CO.)., LTD.). If the retrograde direction guide wire is difficult to insert directly into the guide catheter, or if the direction microcatheter cannot be inserted directly into the guide catheter, it is recommended to use the active greeting technique as soon as possible (active greeting technique, AGT, that is, the Guidezilla catheter, the mother and child catheters have a retrograde direction guide wire that opposes the antegrade guide catheter). In some cases (for example, total occlusion of the initial part of the right coronary artery, total occlusion of the initial part of the left coronary artery, etc.), through a special trap or a homemade trap, you can catch the return guide wire and pull it out of the body frame [21]. During interventional treatment and when removing the RG3 guide wire, it is necessary to cover the microcatheter with the collateral vessel as much as possible in order to prevent the cutting of the guide wire by the collateral vessel, as well as to prevent lesion to the mouth of the coronary artery by the guide catheter in the retrograde. If there is no RG3 guide wire, you can

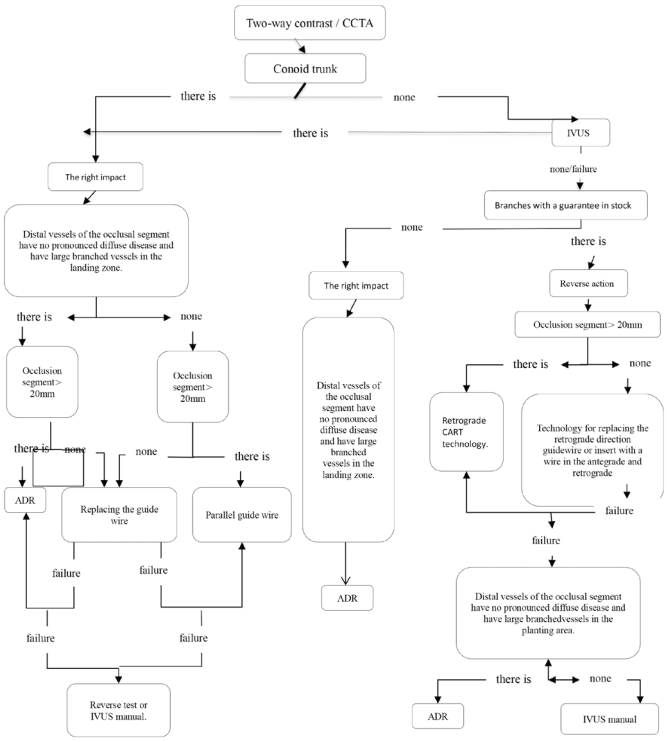
use another 300-330 cm guide wire (but the drilling guide wire or extension guide wire should be avoided), as well as Rendezvous technology (such as microcatheter docking technology) and its advanced technique to complete the PCI operation [43].

Recommended CTOCC CTO -PCI way (Figure 1)

Way 1: In the case of lesions of the CTO with conoid trunks, the initial strategy provides for interventional therapy.

Way 2: The 1st way does not have a severe degree in blood vessels exceeding the occluded segment. If the length of the occlusal segment is greater than 20 mm, ADR technique should be used first, and if the occlusal segment is shorter than 20 mm, interventional therapy should be analyzed first and the guide wire replacement technique should be applied. If the guide wire replacement technique fails, use the ADR technique to unlock the lesion.

Figure 1 - Proposed road scheme of CTOCQ CTO-PCI



Note: CTO, chronic total occlusion; PCI, Percutaneous Coronary Intervention; CCTA, coronary CT angiography; ADR, Antegrade dissection re-entry technology; IVUS, intravascular ultrasound ; retrograde direction CART technology, the technology of finding the antegrade and retrograde directions subintimal path through the control in the opposite direction.

Way 3: If in way 1 there are severe diffuse lesions of the distal vessels of the occlusal segment and / or CTO lesions involving large branched vessels in the landing zone, the length of the occlusal segment is more than 20 mm, analyze antegrade direction interventional therapy and first try parallel guide wires: If the length of the occlusal segment is less than 20 mm, then first you should use the technique of replacing the guide wire. If the guide wire replacement technique failed, you can use the parallel guide wire technique to uncover the lesion.

Way 4: In case of CTO lesions that were not successful by the methods proposed in ways 1-3, retrograde direction interventional therapy or antegrade direction interventional therapy against the background of IVUS is recommended.

Way 5: If the CTO is affected without a cut arc, if possible, it is recommended to use the methods proposed in the ways below 1 to 4 recommended by IVUS.

Way 6: In case of failure to open the lesion to the CTO without a conoid trunk, not equipped with IVUS equipment or the proposed technology of the 5th way, if the collateral vessels are not suitable for use, antegrade direction interventional therapy is recommended. In the event that there are no severe diffuse lesions in the distal vessels of the occlusive segment and/or there is a CTO lesion that does not affect a large branched vessel in the landing zone, it is recommended to use ADR technology in antegrade direction interventional therapy.

Way 7: In case of failure to open the lesion to the SRT without a conoid trunk, not equipped with IVUS equipment or the proposed technology of the 5th way, in the presence of collateral vessels suitable for use, retrograde direction interventional therapy is recommended.

Way 8: In way 7, for lesion of the CTO with an occlusal segment length of more than 20 mm, it is recommended to use first the retrograde direction CART technique during retrograde direction intervention; for lesion of CTO with an occlusal segment length of less than 20 mm, you can use the technology of replacing wires in the retrograde direction or docking antegrade and retrograde directions guide wires. If the above method fails, try the retrograde direction CART technique to unlock the lesion.

Way 9: For a CTO lesion that was not successful with the technique proposed in way 8, if there are no severe diffuse lesions in the distal vessels of the occlusal segment and/or there is lesion to the CTO that did not affected the large branched vessel in the landing zone, ADR technology is recommended: if severe diffuse lesions and/or CTO lesions involving large branched vessels in the landing zone are observed in the distal vessels of the occlusal segment, antegrade direction interventional therapy against IVUS is recommended.

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Review of pharmacological effects of imidazole derivatives

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Abstract

Imidazole derivatives are the perspective class of drugs with a broad spectrum of application in medicine. Imidazole is a nitrogen-containing heterocyclic ring; it has two equivalent forms; hydrogen atom may be located on any of two nitrogen atoms. Imidazole ring may interact with various cations and anions, as well as with biomolecules by different reactions; the presence of various groups in the nitrogenous heterocycle structure makes it possible to identify substances with a broad spectrum of pharmacological effects. They are very important for the production of new drugs and recently draw the special interest of scientists due to their properties in the chemistry and pharmacology. Introduction of highly active Imidazole has stimulated the significant achievements in the field of chemotherapeutic agents and plays the very important role in medicine. Therefore, the active search for highly active Imidazole compounds still continues. This article describes the antifungal and antibacterial effects identified in preclinical studies through a literature review. The purpose of this work is to review the principal effects of Imidazole published in the scientific literature in recent years.

Key words: Imidazole, antibacterial, anti-tuberculosis, antifungal activity

Introduction

One of the modern objectives of medicine is to search for new biologically active substances with high efficiency and low toxicity to the human body. Currently, the complex organic molecule directed synthesis method development studies are carried out in the modern synthetic organic chemistry to obtain physiologically active substances with the selective effect.

Imidazole-containing drugs have a broader spectrum of application in clinical medicine. Imidazole component presents in some pharmacologically important drugs such as Metronidazole, Pretomanid, Ketoconazole, Clotrimazole and Miconazole, Tipifarnib, Megazol, Nafimidon, Losartan, Azathioprine, Dicarbazine, Cimetidine, Naphthyzin and Xylometazoline, Mercazolil and Thiamazole, etc. [1].

Pharmacological effects

It has been established that heterocycles contain the azole ring system and have a broad spectrum of biological properties. Based on various literature studies, Imidazole derivatives have antibacterial, anti-tuberculosis, antifungal, antiviral, anti-inflammatory, antitumor activity, etc. To combat the unprecedented diseases and rising drug resistance worldwide, substituted Imidazoles is the perspective class for new drug development. Numerous Imidazole-based derivatives have been developed, synthesized and evaluated for the biological activity in vitro and in vivo. Some Imidazole-based derivatives have the excellent pharmacological profile [2].

Antifungal effect

In clinical application, azoles are more commonly used to treat yeast and fungal infections, while Imidazole-based antifungals (for example, Miconazole, Econazole, Ketoconazole, and Clotrimazole) and Triazole-based antifungals (for example, Fluconazole and Itraconazole) are the basis for fungal infection treatment. The critical need for new compounds is defined by the development of resistance to the existing antifungal drugs and the high toxicity of some antifungals.

The literature review has shown that many antifungals, containing Imidazole compounds, have two carbons between Imidazole and aromatic moiety [3]. In 2018, N.D. Yakovychuk et al. (Bukovinian State Medical University, Chernivtsi, Ukraine) synthesized new nitro-containing Imidazole derivatives studied in vitro for antifungal activity. Method of double serial dilution in Sabouraud's liquid medium was used; antifungal effects on C. albicans, C. guillermondii,

C. krusei, C. glabrata, C. kefyr, C. tropicalis, C. unscripicua and C. zeylanoides were studied. As a result, 3-methyl-4-[1-(1-naphthyl-4-chloro-1H-imidazol-5-yl)-2-nitroethyl-]-1H-pyrazol-5-ole and 2,4-dichloro-5-(2-nitrovynil)-1-(4-fluorophenyl)-1H-imidazole were the most active substances. 4-chloro-1-imidazole has the lower anti-candidiasis activity, 5-(2-nitrovinyl) Imidazoles and their derivatives had the highest antifungal activity against C. krusei, C. kefyr and C. Unscripicua strains. Nitro-containing Imidazole derivatives had a low antifungal activity against C. tropicalis, C. Guilliermondii, C. albicans, and C. glabrata strains [4].

In 2012, N.C. Desai et al. (Bhavnagar University, India) conducted a study to determine the antifungal activity of 2-((1-(4-(4-(arylidene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl) phenyl)ethylidene)hydrazono)thiazolidin-4-ones. Imidazole was combined with Thiazolidinone in this study. Thiazolidinone ring is the principal structure in various synthetic pharmaceuticals with a broad spectrum of biological activity. It is known that the combination of Imidazole and 4-thiazolidinone may enhance the effects and reduce toxicity. Combination of Imidazole and 4-thiazolidinone impact on antifungal effect was analyzed in this study. Sabouraud's dextrose broth was used for fungal growth in this study; Griseofulvin as the reference preparation was used by bioassay method, namely, the serial dilution of broth. As a result, the combination of Imidazole compound and Thiazolidinone showed a strong inhibitory effect on C. albicans, A. Niger, A. Clavatus [5].

In 2013, Anisetti Ravindernath et al. (University College of Technology, Osmania University, India) studied the combination of benzo[d]imidazolol and tetrahydropyridine. These compounds were evaluated for antifungal activity against C.albicans and A.niger by bioassay plate method (Margery Lindey, 1962) using Fluconazole as the reference preparation. Compounds with the methoxy group on the phenyl ring were toxic for these two fungi. The fungal activity of compounds showed the better activity compared to the reference preparation Fluconazole [6].

In 2018, Nerith-Rocio Elejalde et al. (Universidad Nacional Autonoma de Mexico) synthesized the new 4-aryl-2-methyl-N-phenacylimidazoles. Intramolecular carbon-nitrogen (C-N) bonding is of important interest due to the broad spectrum of applications of N-heterocycles in medicine and industry. Carbonyl group of ketones was used for the reaction with N-(2-hydroxyethyl)imidazoles. New N-substituted imidazoles were tested for antifungal activity against two fungal species, C. albicans and C. neoformans, using the yeast broth microdilution method (M27-A3 of the Institute of Clinical and Laboratory Standards). Results showed that all compounds had a very low effect on C. albicans. But they were active against C. neoformans. Difluorinated compound had the best activity against C. neoformans, followed by the dichlorinated derivative [7].

In 2019, Altindag, Firuze Diyar et al. (Anadolu University, Turkey) developed and synthesized the series of 2-(substituted dithiocarbamoyl)-N-[4-((1H-imidazol-1-yl)methyl)phenyl] acetamide derivatives to combat the growing incidence of drug-resistant fungal infections. Molecular docking method was used to study the action of cytochrome-dependent enzyme P450 - lanosterol-14a-demethylase. Also, ADME studies were carried out; relationship between the activity and the physicochemical properties of the compounds was established. The results of in vitro anti-candida activity study, docking studies and ADME predictions showed that the most compounds had the significant activity against C.albicans and C. krusei [8].

In 2019, Zhao Shizhen et al. developed and studied a series of biphenyl imidazole analogs for in vitro antifungal activity. Many of the synthesized compounds had the good activity against C.albicans, C.tropicalis, C. neoformans. In addition, some compounds showed a low inhibition of various isoforms of human cytochrome P450 and had a low toxicity [9].

Mina Ahmadi, Rahebeh Amiri and Soutodeh Mohammadi (Islamic Azad University, Iran) described new compounds containing phosphorus and Imidazole. Phosphorus ylides are the synthetic targets with great importance in various biological applications. These compounds have some properties such as anti-inflammatory, antitumor, analgesic and antimicrobial properties. The antifungal activity of stable phosphorus and Imidazole complex was tested by the disk diffusion method. Compounds had the activity comparable with fluconazole against C. albicans. However, these compounds were not superior to the reference preparations used against other fungi [10].

Many experiments were carried out in Sabouraud's liquid medium by the double serial dilution method. Yeast cell suspension and fungal spore suspension were used to prepare the inoculum. Suspension concentration was diluted to McFarland standard (1 Zag).

When all works were reviewed, it was concluded that Imidazole derivatives have the high specificity and activity, a broad spectrum of action and a fungistatic effect. Imidazole compounds with other complexes had the antifungal effect mainly on C. albicans, A.niger and C.krusei. Nitro-containing Imidazole derivatives and Imidazoles with a thiazolidinone ring were the most active compounds among the studied compounds.

Antibacterial effect

Based on the literature review, the next most frequent important pharmacological effect of Imidazole derivatives is the antibacterial effect. Identification of this effect is relevant, because after the identification of almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides), these drugs may lose the effectiveness due to the increased microorganism resistance. Currently, treatment failures, associated with multidrug-resistant bacteria, are the global issue for public health.

Such methods as the paper disk diffusion were commonly used for in vitro antibacterial activity study, and the quantitative antibacterial activity was determined by the minimum inhibitory concentration method. Imidazoles were described by their biological activity against various microorganisms. But the physiological action rate is largely determined by the substituent nature. On the one hand, antibacterial activity depends on various hydrophobic substituents on nitrogen atoms. This review contains the examples of combination of Imidazole with metal ions and compounds with antibacterial effect. There are Imidazole-based complexes with different metals that show the various pharmacological effects, including antibacterial activity [11]. For example, antibacterial activity of Imidazole compounds with bactericidal effect in complex with Ag was studied [12]. In 2013, John McGinley et al. (National University of Ireland) synthesized 1-(3-aminopropyl)imidazole and obtained the Schiff base ligands easily coordinated with Ag(I) centers. Studies were carried out against S. aureus, MRSA, E. coli and P. aeruginosa strains. As a result, the most complexes with Ag (I) had the moderate antibacterial activity [13].

In 2019, Achar G et al. (Jawaharlal Nehru Centre, India) conducted the antibacterial study of benzonitrile hexafluorophosphate and coumarin salts substituted with

imidazolium, benzimidazolium and silver complexes against Gram-positive (S. Aureus) and Gram-negative (E. coli) bacteria. Both series of silver complexes showed the antibacterial activity against E. coli, while the antibacterial activity against S. aureus was moderate. Finally, it was concluded that the complex activity is related to the metal center [14].

Copper ions (II) and cobalt ions (II) were combined with Imidazoles to study the antibacterial activity against gram-positive and gram-negative bacteria. Ana Maria Atria et al. (University of Chile, Chemistry and Pharmacy Department) synthesized the copper and cobalt complex with Imidazole derivatives: Diaqua-bis(5-nitroimidazole)-copper(II)-dinitrate (1); Tetrakis(4-phenylimidazole)-copper(II)-dinitrate, solvate ethanol (2); bis(4-phenylimidazole)-bis(acetate)-copper(II) (3); Hexakis(4-phenylimidazole)-cobalt(II)-acetate (4) and bis(2-phenylimidazole)-bis(acetate)-cobalt(11) (5). The antimicrobial activity of these complexes against S.typhi, S.enteritidis, S. enterica, S.aureus, and Listeria monocytogenes was studied in vitro. As a result, complexes (1) and (3) had the bacteriostatic type of action against gram-positive and gram-negative bacteria. Complexes (4) and (5) had the bactericidal effect on gram-positive and gram-negative bacteria. Various action types of complexes depended on the metal located in the complex coordination center. Thus, complexes with the cobalt metal centers had the bactericidal effect, while complexes with the copper metal centers had a bacteriostatic effect [15].

Also, Imidazoles were combined with well-known compounds showed the antibacterial effect. In 2017, Harshad Brahmbhatt et al. (Josip Juraj Strossmayer University, Croatia) synthesized new series of Imidazole derivatives, which were combined with 1H-pyrazole-4carbaldehyde derivatives. Pyrazole had the antibacterial activity. A mixture of bromophenyl, imidazole and pyrazole had the most potent antibacterial effect on staphylococcus, and a mixture of bromine, fluorophenyl, chlorophenyl, imidazole and pyrazole was active against P. Aeruginosa [16].

A series of imidazole-triazole with naphthaldehydes and 1,2-diketones was synthesized according to the study of Sunil Chauhan et al. (2019). The synthesized imidazole-triazole compounds were screened in vitro to study the antimicrobial activity. Activity against S.epidermis and E. Coli was confirmed [17].

Studies of Shoeb M. et al. (2019) described two series of Imidazole derivatives (D-1-D-4) and (D-5-D-8) containing substituted quinolones. As known, quinolone-based drugs are widely used in medicine and have the high antibacterial activity. Subject to this study, the compounds were tested for the antibacterial activity against E.coli, Shigella flexneri, S.aureus and B.cereus. Among the synthesized compounds, D-1 and D-2 had the antibacterial activity against gram-positive and gram-negative bacteria, confirming a broad spectrum of activity. Also, D-8 and D-3 had the antibacterial activity against E.coli, Shigella flexneri and B.cereus. All other compounds had a moderate or mild antibacterial and antifungal activity [18].

In 2019, the results of synthesis and antimicrobial evaluation of triazole containing triaryl-1H-imidazole implemented by Chauhan Sunil et al. were reported. Efficiently synthesized triazoles containing triaryl-1H-imidazole had the significant antimicrobial activity against fungal and bacterial strains. Triazolyl imidazole was significantly effective against P. aeruginosa, A. niger, B. subtilis, S. epidermidis and C. albicans [19].

In 2019, Tanuj Hooda, Sunil Sharma, Naveen Goyal (Uttarakhand Technical University, India) synthesized Imidazole derivatives from carboxylic acid and evaluated the antibacterial activity against B.subtilis, S.aureus, P.aeruginosa, E.color, T.thermophilus by in vitro dilution method. It was identified that three compounds have the bactericidal effect against these bacteria [20].

Bhoomendra A. Bhongade et al. (RAK Medical & Health Sciences University, United Arab Emirates) reviewed imidazol[2,1-b][1,3,4]-thiadiazole compounds. The biological potential of Imidazole[2,1-b][1,3,4]thiadiazole derivatives, such as antimicrobial activity, had been comprehensively studied. Most studies of imidazole thiadiazoles are focused on their in vitro evaluation as the antibacterial agents against some gram-positive and gram-negative microbes. Imidazoles in combination with thiadiazoles had the moderate antibacterial activity against Klebsiella, P.aeruginosa, S.aureus, and E.Faecalis [21].

Most studies, conducted to determine the antibacterial effect on reference strains of gram-positive and gram-negative bacteria, were subject to commonly used methods of double serial dilutions in liquid medium and minimal bacteriostatic and bactericidal concentration determination methods.

As a result, the antimicrobial activity of studied compounds depends on their chemical structure. Studies have shown that the introduction of arid group and thiazolidine fragment into imidazole cycle position reduces the bactericidal activity [22]. Also, the preparation of complex compounds with metal salts showed the effectiveness of the compounds. This has made it possible to enhance the spectrum of action and reduce toxicity. Among complexes of Imidazole with metals, a good effect against S.Aureus and E.Coli is achieved with Ag (I), copper (II) and cobalt (II). Imidazoles with known quinolones and triazoles also had the significant antibacterial activity against S.epidermis and E.Coli, in comparison with other complexes. Study results are the prerequisite for further targeted synthesis of new compounds with predictable antimicrobial properties.

Anti-tuberculosis activity

Despite the recent progress in the treatment of infectious diseases induced by Mycobacterium, these microorganisms still represent a significant problem in global healthcare and the leading cause of death from infectious diseases in the world. In spite of availability of anti-tuberculosis drugs, tuberculosis is still one of the most common infectious of global concern. The current situation is worsened by HIV epidemic led to the increase in multidrug-resistant tuberculosis prevalence and growth of drug-resistant microorganisms [23]. Taking these facts into consideration, it is required to find new therapeutic agents to combat M. tuberculosis infections.

In 2012, Daniel Cvejn, Vera Klimesova, Filip Bures (University of Pardubice, Czech Republic) investigated the antimycobacterial activity of 2-phenylimidazole derivatives obtained from α-amino acids. Among 2-phenylimidazole derivatives, compounds containing a nitro group, had the activity against M. tuberculosis, but this activity was lower than activity of isoniazid. Activity against M. avium and M. kansasii exceeded activity of isoniazid. Availability of nitro group was the essential characteristic affecting the antimycobacterial activity of compounds studied [24].

In 2019, Vasilichia Antoci et al. studied the antimycobacterial activity of bis-(imidazole/benzimidazole)-pyridine derivatives. Anti-tuberculosis analysis showed that the compounds had the bactericidal anti-tuberculosis activity and were not cytotoxic. The results showed that the benzimidazole moieties were more active than the compounds carrying the imidazole moiety.

Chlorbenzoyl moiety compounds associated with benzimidazole showed the most significant antimycobacterial activity. Finally, compounds with chloride or nitro group in the benzene moiety were active [25].

In 2020, Koushik Mukherjee et al. (University of Kalyani, India) studied some Imidazole and piperidine derivatives against Mycobacterium smegmatis to produce anti-tuberculosis drugs. Among the compounds studied, benzyl 1H-imidazole-1-carbodithioate and allylpiperidine-1-carbodiothioate inhibited M. smegmatis better than other compounds. They enhanced the activity of isoniazid or rifampicin used together, and cytotoxicity was low. Activity of these two compounds against mycobacteria at rest was studied and found to be effective [26].

In conclusion, Imidazole compounds mainly containing a nitro group were the most active against M. tuberculosis.

The aforesaid studies of various Imidazole derivatives showed the promising results.

Considering these pharmacological properties of Imidazole, it is expected that these compounds have the effective activity. In addition, the mutual combination of Imidazole ring and various substituents may result in the effect enhancement. Based on the studies conducted in recent years and confirmed the antifungal and antibacterial activity, there are grounds for further study of Imidazole derivatives. In perspective, the addition of new compounds may result in the development of safer and more effective compounds.

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Integrative approach to fracture healing: A review

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Abstract

It is said that first sign of civilization in human history was a femur that had been broken and then healed with the care of the loved ones. Such deep is the association of mankind and fractures. Since time immemorial, fracture patients are taking varied therapies to enhance fracture healing. Some are evidence based, some are not. With renewed interest in complementary and alternative medicine; it becomes wise to make primary care physicians aware of the viewpoints of dietician, homeopathy doctor and an ayurveda doctor on the medicines prescribed by them for fracture cases. A physician should be aware of different treatment methodologies to have an intelligent discussion with a curious patient. Dieticians emphasize on a healthy balanced diet. Ayurveda physicians focus on shali rice and clarified butter; while homeopathy physicians vouch on Symphytum.

Key words: fracture healing, alternative remedies, integrative approach, diet, ayurveda, homeopathy

Introduction

We are witnessing increasing number of fractures with patient's wish to be mobile "as soon as possible". Access to Google, grazing of often contradictory literature and the lickety-split attitude to be functional often led to consultation with practitioners of different therapies.

A medical doctor is often faced with the query of best diet for fracture healing and she/ he often digs out history of Homeopathy/ Ayurveda medication intake with the purpose to enhance fracture healing. So, it's prudent that a primary care physician be aware of the diet that is good for bone health and be aware of the medicines that are prescribed by Homeopathic and Ayurveda doctors for fracture cases.

Fracture healing is a complex process and different mechanisms come into picture while treating a fracture operatively or non-operatively. Diet or any medication cannot be a substitute for an evidence based management of a fracture.

This review has summarized the opinion of a dietician, an Ayurveda doctor, a Homeopathy doctor and opinion of an allopathic physician on routine medications prescribed to ensure timely fracture healing. A physician should be aware of different treatment methodologies to have an intelligent discussion with a curious patient [1].

Role of diet in fracture healing:

A well-planned diet will help a patient build strong bones that are so essential for fracture healing. A patient needs sufficient calcium for bones in the reparative phase and adequate vitamin D for absorption of calcium in the body.

In general, a dietician would advise the following for a patient with a fracture:

1. Eat Lots of Vegetables

Vegetables are rich in vitamin C, which eventually helps in the stimulation of bone-forming cell production. Moreover, the antioxidant effects of Vitamin C may help in protecting bone cell damage as suggested in some studies [2]. Increase in bone mineralization and maintenance of bone mass has been linked to a high intake of fresh seasonal green and yellow vegetables.

2. Consumption of Adequate Protein

For the healing of the fracture, adequate-protein is important. Collagen is the protein that is found in bone in significant percentage. Less intake of protein decreases the absorption of calcium, thereby affecting rates of formation of bones and its breakdown [3]. But, protein more than 100 grams on daily basis can lead to leaching of calcium from bones in response to rising acidity in the bloodstream. Nevertheless, it can be avoided as long as there is a balance of enough calcium intake along with

plenty of plant foods in the diet [4].

3. Daily consume calcium-rich foods

The most vital mineral for healthy bone is calcium, and it is the chief mineral present in bones. Daily consumption of calcium for the protection of the bone structure and its strength is important because of the continuous breakage of bones and their replacement with new ones. 1,000 mg per day is the Indian Recommended Daily Allowance (RDA) for Calcium [5].

Calcium's good sources are:

a) Milk, paneer, buttermilk, and other dairy products
b) Green leafy vegetables, like cabbage, broccoli
c) Soya beans
d) Tofu
e) Nuts
f) Bony part of fish, such as sardines

Though, the absorption of calcium in the body varies greatly. It is always good to include calcium in the diet throughout the day e.g. include one high-calcium food in every meal from the above list.

4. Take enough amount of Vitamin D and Vitamin K

Fat-soluble vitamins like Vitamin D and vitamin K are enormously important for the healing of fractures. Vitamin D has many roles in bone health which includes absorption of calcium. We may be deficient in Vitamin D, as it is not easy to get it from our diet and by the action of the sun exposure (without sunscreen on our skin). Good dietary sources of Vitamin D are:

a) Food products like milk and oils fortified with Vitamin D
b) Eggs
c) Salmon, sardines and mackerel type oily fish

Vitamin K2 alters osteocalcin, which is a protein involved in bone formation. This alteration aids osteocalcin to fix minerals in bones which helps in prevention of the calcium loss from bones [6]. MK-4 and MK-7 are the most common forms of Vitamin K2. MK-4 is found in liver, eggs, and meat in small amounts. MK-7 exists in fermented foods like cheese and fermented soybean products.

5. Avoid Very Low-Calorie Diets

Following a low-calorie fad diet is not a good idea or an achievement, particularly for fracture healing. It slows down metabolism, creates rebound hunger, causes loss of muscle mass and it can damage bone health. Strong bones are built and maintained by following at least 1,200 Kcal well-balanced diet every day. Bone health is supported by adequate protein and a diet rich in vitamins and minerals.

6. Consume foods rich in Omega-3 Fats

Anti-inflammatory effects are produced by omega-3 fatty acids in the diet. An adequate balance of omega-6 to omega-3 fats is equally important in addition to having omega-3 fatty acids in the diet. One should look forward to a 4:1 or lower ratio for an omega-6 to omega-3.

Food sources of omega-3 fats include fenugreek seeds, fenugreek leaves, soya beans, red beans, flaxseeds, nuts such as almonds, walnuts; seafood and other fishes (specifically cold-water fatty fish, like mackerel, sardines, tuna, salmon, and herring); plant oils like soybean oil, canola oil.

Omega-6 fatty acids are a kind of polyunsaturated fat that naturally occurs in vegetable oils, seeds, and nuts.

Role of Ayurveda therapy in fracture healing:

Various Ayurveda Formulation for Internal and External Administration-

1. Intake of Ghrit ksheer (Clarified butter and milk) along with drugs of Kakolyadi gana (herbal drugs of particular gana (group), Laksha (Lecca) and Ghrita (Clarified butter) for fracture patient [7].

2. Manjishtha (Indian Madder), Mulethi (Licorice), Red Sandal macerated with Shatdhaut Ghrita (100 times washed Clarified butter) and Shali Rice (a type of rice) should be applied over the fractured portion [8].

3. Sheetal kashaya (water decoction) made of Nyagrodadi gana or Dugdha Sadhita (heated with milk) with Laghupanchmoola should be used for external shower [9].

Ayurveda diet for a fracture patient-

Acharya Shushruta (an ancient sage) mentions that intelligent physician should advice the patient of fracture to take Shali rice, Meat soup, Milk, Clarified butter, Pea's soup and nourishing food and drinks. Patient should avoid use of Salt, Citrus, Pungent food, Alkali food, avoid indulgence in sexual activity, avoid strenuous work and dry foods [10].

Role of Homeopathy therapy in fracture healing

Homeopathy is a therapeutic system which was founded by a German physician Christian Friedrich Samuel Hahnemann (1755 – 1843). Homeopathy is considered a branch of medical science which is based on the principle that diseases can be cured by strengthening the defense system with the substances selected for their properties to develop similar kind of symptoms if given in crude form [11].

In day to day clinical practice, Homeopathy is widely used in the fracture-repair. Homeopathy helps by accelerating the healing of fractures and it enhances callus formation and reduces pain.

In 1992, H. Zeeden in 1992 presented 5 cases to demonstrate the benefit of Symphytum officinale in factures [12]. These cases included a delayed union case of a fracture of os naviculare, a fatigue fracture case and a case of post-traumatic pseudarthrosis of sternum. Similarly, in 2008 and in 2010, Sakakura and colleagues showed that Symphytum officinale enhances osseointegration and bone formation around the titanium implants of tibiae of rats [13, 14].

In 1994, Oberbaum et al. conducted a study on guinea pigs. Bone fractures were induced and then Arnica and Symphytum were administered. The study showed that there was significant increase in mineralization of new bone at the site of factures in homeopathically treated group in comparison to the group treated by placebo [15].

In a classical Homeopathic prescription, patient's physical as well as mental symptoms are taken into account. So, same medicine can be prescribed in different clinical conditions and different remedies can be given to apparently similar clinical pictures and different mental pictures of patients. However, it has been seen that there are certain medicines which works specifically in cases of fractures. Arnica, Calcarea Phos, Symphytum and Hypericum are such medicines which are used widely.

Arnica Montana can be given in the first days to reduce the swelling and pain at the fracture site. Calcarea Phos can be the choice of remedy if reunion and healing is delayed. Symphytum is widely used to enhance callus formation, to reduce pain and fasten the reunion. Hypericum is used in the nerve rich areas.

Calcium and vitamin D supplements for fracture healing:

It's an established concept that vitamin D has a role in fracture healing [16]; but, available data are too uneven to

illuminate how and in what manner [17, 18] Cholecalciferol (Vit D3) is the most frequently prescribed Vitamin D form. 1 μg of cholecalciferol is equivalent to 40 IU of vit D. It is usually given as 60,000 IU in 1 g granules every week for 3 months. Calcitriol 0.25μg orally on alternate days is the next frequent prescription of Vitamin D. But, hypercalcemia has to be watched for this drug [19].

Calcium supplements usually in the form of Calcium carbonate (40% Ca) 500 mg twice a day is prescribed for fracture patients. These supplements are usually well stomached; only gastrointestinal side effects like constipation, bloating and excess flatulence (especially with calcium carbonate) have been described. But, it has been reported that if diet is suitable these calcium supplements does not accelerate fracture healing [20].

Conclusion:

Overall, physicians (particularly of developing world- as these therapies are used more often in this part of the world) must be aware of these complementary and alternative medicine (CAM) for fracture healing [21]. A knowledge of these therapies will ensure a cognizant expression of physician in front of the patient. Knowledge of CAM would encourage physician to specifically ask patients about usage of these therapies and would ultimately lead to enhanced confidence of patient onto his/ her physician.

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Quality of life assessment in chronic viral hepatitis

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Abstract

Chronic viral hepatitis has a significant impact on morbidity, quality of life and mortality and is characterized by a growing economic and social burden in the context of disability of the population and an increase in life expectancy. Chronic viral hepatitis can significantly worsen health-related quality of life indicators (HRQoL), which are a reflection of the influence of the disease and therapy on the physical and emotional components of the patient's health, especially in patients with progressive liver disease and/or active viral activity. To assess the quality of life related to health, you can use general tools and tools for specific diseases. Common tools available in the scientific literature include the Short Form 36 questionnaire (SF-36) and the Euroqol five-point questionnaire (EQ-5D). However, since general instruments cannot always detect the subtle effects of a particular condition on the quality of life, the use of special instruments is of great value, due to their ability to clinically characterize the quality of life in patients with chronic viral hepatitis. The use of recently developed special tools for assessing the quality of life will greatly assist in the verification of preventive and therapeutic interventions in this area. One of the priorities of any measures for the prevention and treatment of chronic viral hepatitis is to improve the quality of life in this category of patients.

Key words: chronic viral hepatitis, health-related quality of life, mental disorder, depression, antiviral treatment

Introduction

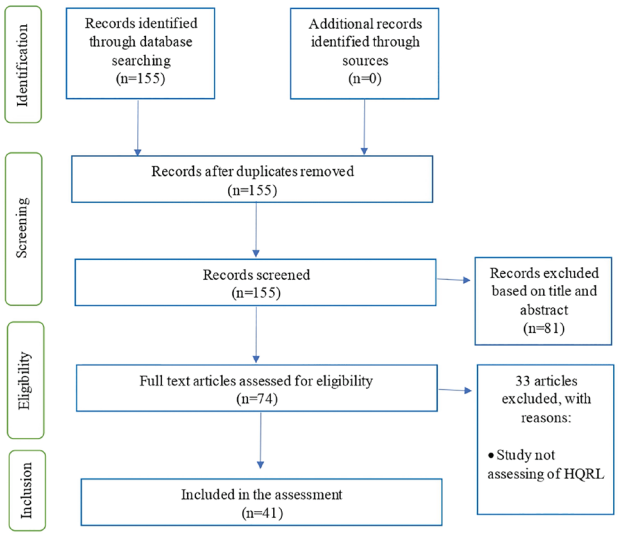
Viral hepatitis plays a significant role in the structure of diseases of the digestive system, characterized as one of the global socially significant problems that affects the lives of hundreds of millions of people around the world and is a source of steadily progressive morbidity and mortality. Most of the burden of hepatitis falls on viral hepatitis B and viral hepatitis C, which tend to chronic infection and are characterized by inflammatory processes in the liver, capable of eventually trasformation into fibrotic and cirrhotic changes [1,2]. According to the latest estimates, more than 257 million people in the world have active HBV infection, and according to some researchers, the number of infected patients reaches 350 million, from 71 to 185 million people have HCV infection [1,3,4]. One of the most severe forms of chronic viral hepatitis is chronic viral hepatitis D, which can often develop to liver cirrhosis and hepatocellular carcinoma [5]. A necessary condition for the manifestation of pathogenicity in chronic viral hepatitis D is the simultaneous presence of HBV infection [6]. Thus, according to the latest data, worldwide 5% of chronically infected patients with HBV are also infected chronic viral hepatitis D, which is estimated to be 20 million people with HDV infection [7].

Cognitive function disorders and neuropsychiatric disorders are registered in almost 50% of patients with HCV infection, which do not depend on the severity of liver disease or the rate of replication of HCV infection [8]. In addition, symptoms such as chronic fatigue, sleep disturbance, depression and decreased quality of life are usually associated with neurocognitive changes in patients with non-cirrhotic chronic HCV infection, regardless of the stage of fibrosis, the infecting genotype and in the absence of structural brain damage or signal abnormalities with conventional magnetic resonance imaging of the brain [9].

The present review aims to investigate the quality of life of patients with chronic viral hepatitis. A systematic literature search of English-language studies was performed in Medline, Embase, Web of Science, Scopus and The Cochrane Library from January 2016 to February 2022. The systematic literature search resulted

in 155 hits. The screening of titles and abstracts identified 74 potentially eligible articles. Finally, 41 studies were included in this review. The selection algorithm is shown in Figure 1.

Figure 1 - Flow diagram of the of the literature search



Health-related quality of life and fatigue in patients with chronic hepatitis

The presence of chronic diseases in patients can have a negative impact on the well-being of patients, both psychologically and physically. Thus, chronic HCV-infection can significantly worsen the indicators of health-related quality of life (HRQoL), which are a reflection of the influence of the disease and therapy on the physical and emotional components of patient's health, especially those with advance liver disease and/or active viral activity [10,11]. According to researchers, patients with chronic viral hepatitis develop symptoms of anxiety and/or depression, which also has a strong impact on their health-related quality of life [11]. In a study conducted in Greece, high levels of anxiety and depression were recorded among patients with choleric viral hepatitis, as well as the overall health-related quality of life ($p<0.001$). At the same time, female sex and damage to the liver parenchyma were associated with a higher level of anxiety ($p<0.05$) [11]. In a recent study, it was found that the most common extrahepatic manifestations are diabetes mellitus (in 15% of patients) and depression (in 25% of patients). These HRQL data showed that chronic viral hepatitis has a negative impact on overall physical and mental health [12]. It has been established that patients with chronic HCV infection may experience other symptoms that worsen the quality of life, such as fatigue and neurocognitive disorders. In the early stages of HCV disease with minimal inflammation of the liver, patients may have pronounced symptoms of depression, fatigue, neurocognitive deficiency than in the general population [12].

Depression is a frequent disorder reported in one third of patients with HCV infection and may be a reaction to increased psychosocial stress, as well as physical symptoms of progressive chronic viral hepatitis C or concomitant diseases [13,14]. Thus, the prevalence of depression is estimated to be 1.5-4.0 times higher than in patients with chronic viral hepatitis B [14]. Researchers report that the non-modern diagnosis of mental disorders can not only significantly reduce the already rather poor quality of life, but lead to non-compliance with recommendations and drug therapy regimens, which can lead to poor treatment results. These disorders, in the absence of their therapy, contribute to a higher level of risky behavior among patients, which can pose a danger both to the patients themselves and to the healthy population [15]. In patients with chronic viral hepatitis B, depression is also considered one of the most common mental disorders that has an adverse effect on the progression of the disease. Although, there are currently limited studies on the assessment of depression in patients with chronic HBV-infection [16]. The results of a recent study showed that 37.5% of patients with chronic hepatitis had depressive symptoms, 31.4% of patients had minimal depressive symptoms. According to the multivariate logistic regression, it was found that higher age, lower income, unemployment, living with a spouse/partners had a positive association with the presence of depression. At the same time, the presence of physical health problems and a lower quality of life associated with health were closely associated with a higher risk of depression [16]. Data of researchers from China have shown that the quality of life in patients with chronic viral hepatitis B depends on the presence of cirrhosis. Thus, the results showed that the physiological quality of life of HRQoL in the group with cirrhosis was significantly lower than in the group without cirrhosis (P=0.003), while psychological HRQoL was also lower (P=0.006) and had a significant negative correlation with liver stiffness (P=0.001). Additional independent factors associated with poor quality of life HRQoL in patients with HBV-related cirrhosis were positive HBV DNA viral load (OR=6,296, P=0.041), family history of hepatocellular carcinoma (OR=36,211, P=0.001) [17]. Comparing the quality of life in patients with chronic viral hepatitis C and chronic viral hepatitis B, researchers found that patients with HCV have lower indicators when using the SF-36 quality of life questionnaire, indicators of memorization of words, in recognition of figures and in terms of alertness and working memory [18]. The patients with chronic viral hepatitis C have lower life indicators and these data are confirmed by the results of other researchers. Thus, in the conducted study, it was found that 85% of patients with chronic viral hepatitis C had chronic fatigue, 50-60% of patients had mild depression or anxiety, 45% memory deficit and 30% attention deficit, regardless of their HCV viremia status or treatment history [19].

Chronic viral hepatitis D is the most severe form of chronic hepatitis, which is characterized by the most rapid development of liver cirrhosis, liver failure and hepatocellular carcinoma compared to HBV monoinfection. Despite all this, there are still difficulties in its diagnosis and in the absence of its standardized treatment [20,21]. As a result of a review of the existing literature, we found reports of health-related quality of life in chronic hepatitis B and HCV-infection, but no studies of outcomes reported by patients with chronic viral hepatitis D. But few studies have shown that HDV infected patients reported worse outcomes in psychological areas, such as anxiety and emotional well-being, as well as in physical areas, such as abdominal symptoms, physical well-being and impaired activity, compared with patients with chronic viral hepatitis D [22].

Another of the common and main signs of chronic viral hepatitis affecting the quality of life is sleep disturbance. Other researchers also confirm the fact that the violation of the quality of life is more pronounced with the progression of the disease [23].According to the latest data, 60-80% of patients with chronic liver diseases have problems with sleep, which manifest themselves in the form of insomnia, a decrease in the quality and time of sleep, an increase in the duration of latent sleep, prolonged daytime drowsiness, restless legs syndrome [23].

The quality of life of HRQoL in patients with chronic viral hepatitis remains low and depends on many factors, such as the presence of cirrhosis, viral load, concomitant pathology.

HRQoL can be improved through the use of antiviral therapy, which prevents the progression of cirrhosis [24]. In addition, the eradication of hepatitis viruses improves a wide range of extrahepatic manifestations and improves the quality of life [25]. Elimination of the hepatitis virus with the use of antiviral drugs leads to a significant and long-term improvement in the quality of life of HRQoL in patients [26]. Although, according to some researchers, the quality of life of patients with chronic viral hepatitis still remains lower than that of the general population. Despite the elimination of the virus, patients still have primary problems in normal activities and anxiety/depression. Therefore, the study of information about these ongoing problems, despite treatment, serves as a guide for medical interventions and follow-up of the patient [27].

Assessment of quality of life in chronic viral hepatitis

Currently, it is believed that health-related quality of life (HRQoL) serves as a subjective assessment of the impact of illness and treatment on the physical, psychological, social and somatic spheres of functioning and well-being in patients [28]. Currently, HRQoL general tools are actively used in clinical practice, which are intended for use in a wide range of population groups and interventions. The main feature of these tools is simplicity and efficiency. All of these tools are designed to explore areas of quality of life that are expected to be affected by medical interventions. According to this quality, they are widely used in observational and clinical studies, because they allow comparing, for example, different groups of the population suffering from the same disease or comparing the effect of the disease on the quality of life depending on the condition of the disease [29].

One of the publicly available tools in the scientific literature is the short form 36 questionnaire (SF-36) and the Euroqol five item questionnaire (EQ-5D), which are the two most popular questionnaires used to quantify the quality of life associated with health in patients with chronic viral hepatitis [30,31]. The SF-36 questionnaire consists of 36 items, in which 8 health-related areas of health quality are measured (physical functioning, role restriction due to physical problems, bodily pain, general health, vitality, social functioning, role restriction due to emotional problems and mental health) [30]. Using the EQ-5D questionnaire, it is possible to register the level of problems reported by patients themselves in accordance with five parameters (mobility, self-care, normal activity, pain/discomfort and anxiety/depression) [31].

Studies using SF-36 were conducted in patients with chronic hepatitis B on the background of antiviral treatment and without treatment [32], in patients with chronic hepatitis C receiving interferon-free therapy [33], after treatment of chronic hepatitis C viral infection with direct-acting antiviral drugs [34]. In a study involving 102 patients with chronic viral hepatitis B, the quality of life associated with health was assessed against the background of antiviral treatment and without treatment. Thus, the results showed that in the treatment group SF-36 showed that physical functions improved significantly compared to the treatment discontinuation group [32]. EQ-5D was used in the treatment of direct-acting antiviral drugs in patients with chronic hepatitis C [35], when studying the real impact of direct-acting antiviral therapy on the health-related quality of life of people with HIV and chronic viral hepatitis C co-infection [36]. In the Canadian cohort study of HIV and HCV coinfection, in which 1795 participants from 18 centers participated prospectively, participants initiated oral responses of the using direct acting antiviral therapy. The results showed improvements in HRQoL in sustained viral response [36].

One of the disadvantages identified when using common questionnaires is that they are not sensitive enough to determine the quality of life of HRQoL to specific a particular disease. Researchers recommend to supplement general tools with questionnaires specific to this disease in order to obtain more accurate results of quality of life in patients with chronic viral hepatitis [10].

Specific tools to assess quality of life in chronic viral hepatitis

Due to the fact that common instruments may not always detect subtle effects of a certain condition on the quality of life, the use of special tools can give more accurate results in assessing the quality of life associated with health in patients. There are already a number of tools in the field of health assessment in chronic viral hepatitis.

So, one of the important special tools for studying the quality of life is the questionnaire of chronic liver diseases (CLDQ), designed for specific liver diseases. It is a reliable and reliable tool for assessing the quality of life of HRQOL in patients with chronic viral hepatitis. The results of a study conducted in Japan indicate that HRQOL in patients with chronic viral hepatitis mainly worsens due to emotional factors, not somatic symptoms [37]. One of the subtypes of the questionnaire developed recently is CLDQ-HBV, which is a short, specific tool for assessing the quality of life in patients with chronic viral hepatitis B [38] and Chronic Liver Disease Questionnaire-Hepatitis C (CLDQ-HCV) the hepatitis C virus-specific quality-of-life instrument [39]. These tool models have been developed and validated using a large data set and an established methodology that demonstrates excellent psychometric characteristics and has excellent accuracy at the group level [38,39]. Another tool actively used in assessing the quality of life in patients with chronic viral hepatitis is the FACIT-F questionnaire. This questionnaire is a tool used to determine the outcomes reported by patients and is focused on fatigue, including 4 domains of well-being (physical, emotional, social and functional) and a fatigue subscale. It has the form of a scale from 0 to 160, in which the higher the score, the higher the HRQoL [40]. Thus, in a recent study, the overall FACIT-F score in patients with chronic viral hepatitis D was 129.4±24.5 and 136.8±14.2 in patients with chronic viral hepatitis B ($p=0.4416$), which indicated poorer physical well-being ($p=0.0036$) and emotional well-being ($p=0.0541$) in patients with HDV-infection [22]. The WPAI questionnaire identifies specific health problems and is used to assess violations of patients' daily activities and labor productivity associated with HDV or HBV infections in patients. It includes two domains, the first domain «Violation of labor productivity» characterizes the sum of the domains "absenteeism" (loss of hours of work) and "presenteeism" (self-report on a decrease in productivity during work), it is evaluated only if the patient is working, the second domain «Violation of activity» determines the violation of daily activities in all participants, regardless of their employment status [22]. WPAI results are expressed as a percentage, with higher numbers indicating greater degradation and lower performance [22]. In many studies, the 5D-itch scale has been used, which includes a description of the perception of itching caused by the disease, as well as to monitor the results of the treatment [41]. This questionnaire is a one-page questionnaire that classifies patients with itching according to 5D, in particular with duration, degree, direction, distribution and disability. Scores below 5 mean no itching, while 25 points mean having the most severe itching [41].

All of the above special tools have the ability to most accurately characterize the quality of life in patients with chronic viral hepatitis and the ability to assess its changes over time. Another advantage of special tools is the ability to assess the quality of life of patients during therapy and its effectiveness. The disadvantage of specific tools is that they do not make it possible to compare the quality of life of patients with chronic viral hepatitis with other types of population.

Conclusion

Chronic viral hepatitis are the main diseases that can affect morbidity, quality of life and mortality, which can lead to increased health care costs for society. Health-related quality of life (HRQoL) is an important indicator for evaluating the treatment and prognosis of patients with chronic viral hepatitis, and it often has low indicators. The quality of life of patients with chronic viral hepatitis is affected by various factors, among which are the severity of the disease, clinical symptoms and low self-efficacy, affecting the quality of life of patients. Timely screening and treatment of patients with chronic viral hepatitis would be very cost-effective and would significantly reduce morbidity and mortality. The use of special tools designed to assess the quality of life associated with chronic viral hepatitis can significantly contribute to the verification of such interventions.

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Informant-based questionnaire for early detection of cognitive disorders in the olders in Kazakhstan

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Abstract

Aim: The purpose of this study was to identify cognitive disorders in older people by conducting a survey of their relatives (close people) by the Arizona Questionnaire.

Material and methods: The study involved people who had relatives (close ones) aged 60-74 years old. Three hundred and eighty respondents took part in the survey.

Results: Summing up all the points obtained during the survey of relatives 4-13 points 78.7% (n=299), which may indicate the presence of moderate cognitive disorders that are better not to be ignored (suggests going to the doctor) and above 13 points 6% (n=23) indicates a fairly high probability of dementia (urgent need to seek medical help). Our study revealed that family status (p<0.001), employment (p=0.014), and recitation of namaz (p=0.009) act as protective factors that promote social participation and build cognitive reserve. Social isolation, on the other hand, can lead to apathy, withdrawal, depression, and a greater likelihood of cognitive impairment. We also found that place of residence (p<0.001) and living conditions (p=0.002), may also influence the early formation of cognitive dysfunctions. Arizona Questionnaire has high sensitivity and specificity in detecting both mild cognitive impairments and Alzheimer's disease and allows clinicians to quickly and accurately assess people with reported cognitive problems.

Conclusion: As a result of survey informants, it was revealed that most of the olders, whose relatives have been surveyed, may be at risk of cognitive impairment and further testing is needed.

Key words: informant, early detection, cognitive impairments

Introduction

Patients with cognitive impairments seek help from a general practitioner for whom, unfortunately, the time allocated for an appointment has time limits, respectively, a timely full examination and diagnosis of the patient's existing disorders suffers. This leads to the fact that cognitive impairments not diagnosed at an early stage are aggravated and already more difficult to correct. The use of cognitive impairment detection tools such as the Mini Mental State Examination (MMSE) will allow rapid screening and timely patient care. However, the results of screening can be influenced by the level of education of patients or their family members, since people with different degrees of education differ in mentality, level of judgment and that "can lead to false positive impairments for people with a low level of education and false negative without impairment for highly educated people" [1].

Clinicians can use the informant questionnaire for early detection of cognitive disorders [2,3]. The questionnaire for the informant provides for testing not the patient himself, but his close relatives, which speeds up the process of identifying cognitive disorders and is less susceptible to "socio-cultural biases" [4]. It is intended to be used as a selection tool to identify individuals in need of further evaluation. The rationale for weighing certain items in the AQ is that they reflect

the presence of cognitive symptoms that make it possible to predict the clinical diagnosis of AD. Given that subjective memory complaints are common among the elderly, the use of weighted elements can help to more accurately identify people with disabilities. AQ is not intended to replace a full diagnostic examination, which is carried out when assessing cognitive problems. The AQ (Alzheimer's Questionnaire) or the Arizona Questionnaire, proposed by American scientists in 2012, is used to quickly and easily interview close relatives of older people to detect cognitive impairments. The entire testing procedure takes 3 minutes. The test, according to American scientists, correlates with neuropsychological tests, is "a reliable indicator of cognitive impairment and accurately identifies Alzheimer's disease (AD) and moderate cognitive impairment (MCI), is easily interpreted and helps to identify cognitive impairment at an early stage in 90% of cases" [5,6]. It is known about the conduct and publication of a number of studies confirming the diagnostic accuracy and psychometric reliability of the Arizona Questionnaire [7]. The superiority of AQ over objective cognitive tests and comparability with other questionnaires based on informants and patients are also shown [8,9].

Material and methods

The study involved relatives (close people) of elderly people aged 60-74 years, point-selected from all over Kazakhstan, who voluntarily agreed to participate in the survey. The exclusion criteria were, respectively, people without relatives aged 60-74 years, refusal to participate in the study, the presence of mental illness.

The AQ was used for the survey. The AQ is an assessment of dementia, consisting of 21 items. AQ items are divided into five areas, including memory, orientation, functionality, visual-spatial and language perception. Tasks are presented in a "yes / no" format, with the total score for the "yes" tasks equal to the total score from 0 to 27, with higher scores corresponding to a greater impairment [10]. One of the 21 items in our survey was uninformative due to the fact that the respondents noted that their relative (close person) does not drive a car. Therefore, we excluded the question “Are there any problems with driving a car?” from the questionnaire, and as a result, 20 questions were left for the survey. The interpretation of the results of the survey of respondents about the presence of cognitive disorders in their elderly relatives (close people) is shown in Table 1.

Table 1 Interpretation of survey results

Total score for the survey	Interpretation of the result
less than 4 points	lack of significant cognitive problems
4-13 points	may indicate the presence of mild cognitive impairment, which is better not to ignore (requires access to a doctor)
above 13 points	shows a relatively high probability of dementia (an urgent need to seek help from a doctor)

Also, in parallel, with the help of a survey of the elderly themselves, their socio-demographic data were collected, such as age, gender, nationality, marital status, education, whether they are currently working, current living conditions, hobbies, alcohol consumption, smoking attitude, namaz reading in the case of muslims, church attendance, prayer reading in the case of the orthodox, the place of residence.

The Ethics Committee of the Semey Medical University (Semey, Kazakhstan) approved our study before it began (protocol №2 of October 18, 2019).

Before the survey, informed consent was obtained from the respondents. The protection of individual data of study participants is guaranteed. Participants were encoded with a unique code.

Statistical analysis

Descriptive statistics were used to analyze the data. For qualitative data, Pearson's chi-square was used. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS version 20.0 (IBM Ireland Product Distribution Limited, Ireland).

Results

A survey of elderly people was conducted. The study involved 380 respondents. The survey results are presented in Table 2.

It can be seen from the Table 2, nearly half of respondents 49.7% (n=189) gave positive answer to the question: "Does the patient have memory loss?" For the question “If so, is their memory it worse than a few years ago?” 44.7% (n=170) answered “yes” (1 point). Less than half of the respondents 43.4% (n=165) answered that an elderly relative repeats the same question or expresses the same idea several times during the day. The majority of respondents 79.2% (n=301) said that their relative does not forget about scheduled meetings or events. Almost a third of the survey participants, 32.1% (n=122), replied that their elderly relative puts things in unusual places more than once a month. The majority of respondents 93.7% (n=356) noted that their close one does not suspect them of hiding or stealing his things when he cannot find them. Most of participants, 94.2% (n=358), answered that their elderly relative does not often experience difficulties when trying to remember the current day of the week, month, year. Many respondents 64.2% (n=244) noted that their elderly relative had cases when he/she could not remember whether he/she had already taken the medicine. 82.9% (n=315) of the survey participants answered that their relative did not have any difficulties when using household appliances, telephone, or television remote control. Also, 85.8% (n=326) of the respondents answered that their elderly relative does not experience any difficulties doing housework. It is good that the majority of respondents 90.3% (n=343) noted that their elderly close ones has not lost interest in their usual hobbies. Only 0.8% (n=3) of the participants noted that their elderly relative could get lost in familiar territory. Almost all respondents 96.1% (n=365) answered that their close one did not lose the sense of the right direction of movement. Slightly more than half of respondents 52.9% (n=201) answered that there are cases that their close one not only forgets names, but also cannot remember the right word. At the same time, 71.1% (n=270) of the respondents noted that their close one confuses the names of relatives or friends. But almost many respondents 88.2% (n=335) answered that their close one has no problems recognizing familiar people.

Table 3 Results of the survey to identify problems in the cognitive sphere

Total score for the survey	% (n)
less than 4 points	15,3% (58)
4-13 points	78,7% (299)
above 13 points	6% (23)

Table 3 shows the final results of the survey to identify problems in the cognitive sphere.

Correlation analysis between the age of older persons and the scores obtained as a result of interviewing relatives (close persons) showed a statistically significant, direct, weak

Table 2 Answers of respondents to the questions of the questionnaire

№	Question	Yes		No	
		% (n)	score	% (n)	score
1	Does the patient have memory loss?	49,7% (189)	1	50,3% (191)	0
2	If so, is their memory it worse than a few years ago?	44,7% (170)	1	55,3% (210)	0
3	Does the patient repeat questions OR statements OR stories in the same day?	43,4% (165)	2	56,6% (215)	0
4	Have you had to take over tracking events OR appointments? OR Does the patient forget appointments?	20,8% (79)	1	79,2% (301)	0
5	Does the patient misplace items more than once a month? OR Does the patient misplace objects so that he or she cannot find them?	32,1% (122)	1	67,9% (258)	0
6	Does the patient suspect others are moving, hiding or stealing items when they cannot find them?	6,3% (24)	1	93,7% (356)	0
7	Does the patient frequently have trouble knowing the day, date, month, year, time? OR Does the patient have to use cues like the newspaper or the calendar to know the day and date more than once a day?	5,8% (22)	2	94,2% (358)	0
8	Does the patient become disoriented in unfamiliar places?	40,3% (153)	1	59,7% (227)	0
9	Does the patient become more confused outside the home or when traveling?	27,1% (103)	1	72,9% (277)	0
10	Excluding physical limitations (e.g., tremor, hemiparesis, etc.), does the patient have trouble handling money (tips, calculating change?)	7,6% (29)	1	92,4% (351)	0
11	Excluding physical limitations (e.g., tremor, hemiparesis, etc.), does the patient have trouble paying bills or doing finances OR Are family members taking over finances because of concerns about ability?	18,2% (69)	2	81,8% (311)	0
12	Does the patient have trouble remembering to take medications or tracking medications taken?	64,2% (244)	1	35,8% (136)	0
13	Is the patient having trouble using appliances (e.g., microwave, oven, stove, remote control, telephone, alarm clock)?	17,1% (65)	1	82,9% (315)	0
14	Excluding physical limitations, is the patient having difficulty in completing home repair or other home related tasks (housekeeping)?	14,2% (54)	1	85,8% (326)	0
15	Excluding physical limitations, has the patient given up or significantly reduced activities such as golfing, dancing, exercising, or crafts?	9,7% (37)	1	90,3% (343)	0
16	Is the patient getting lost in familiar surroundings (own neighborhood)?	0,8% (3)	2	99,2% (377)	0
17	Does the patient have a decreased sense of direction?	3,9% (15)	1	96,1% (365)	0
18	Does the patient have trouble finding words other than names?	52,9% (201)	1	47,1% (179)	0
19	Does the patient confuse names of family members or friends?	71,1% (270)	2	28,9% (110)	0
20	Does the patient have difficulty recognizing people familiar to him/her?	11,8% (45)	2	88,2% (335)	0

relationship (R=0.156; p=0.002). Using the Chi-square test, a statistically significant relationship was found between the scores obtained as a result of the survey of relatives (close persons) with the marital status of older persons ($\chi2$=109.849; p<0.001), their education ($\chi2$=38.324; p<0.001), place of residence ($\chi2$=22.973; p<0.001), current living condition ($\chi2$=12.815; p=0.002), whether he/she currently works ($\chi2$=12.428; p=0.014), reading of namaz by muslims ($\chi2$=9.478; p=0.009) and reading prayer by orthodox ($\chi2$=9.953; p=0.007).

Discussion

As shown in the Table 3 below 4 points were noted in 15.3% (n=58), which indicates the absence of significant problems in the cognitive sphere in elderly people who are relatives of the respondents; 4-13 points - 78.7% (n=299), which indicates the presence of moderate cognitive impairments, which are better not to be ignored (suggests going to a doctor) and above 13 points - 6% (n=23), indicates a fairly high probability of dementia (it is necessary to urgently seek medical help).

Our study revealed that family status (p<0.001), employment (p=0.014), and recitation of namaz (p=0.009) act as protective factors that promote social participation and build cognitive reserve. Social isolation, on the other hand, can lead to apathy, withdrawal, depression, and a greater likelihood of cognitive impairment. We also found that place of residence (p<0.001) and living conditions (p=0.002), may also influence the early formation of cognitive dysfunctions. Cognitive reserve, on the other hand, allows the brain to compensate for the negative effects of disorders that lead to the death of brain neurons, and postpones the development of cognitive impairment.

In our study, we used the AQ. The survey of respondents revealed the absence of significant cognitive problems in 15.3% of their elderly relatives (close people), which is confirmed by research of scientists from China, Arizona and the United States [5,11,12]. Many studies have confirmed the usefulness of using AQ for the early detection of MCI [11]. In the study of scientists from Arizona, AQ demonstrated high sensitivity and specificity for detecting MCI. AQ is a powerful awareness-based tool for identifying cognitive impairments that can be easily implemented in clinical practice. A study conducted in Taiwan showed that most of elderly relatives (close people) had moderate cognitive impairment, and a smaller number of them already had a high probability of developing dementia [13]. It was also confirmed in our study, according to the results of the survey, the presence of moderate cognitive impairment in elderly relatives was revealed. However, a small number of people have a fairly high probability of dementia. In their study, Malek-Ahmadi et al. show that certain cognitive symptoms reported by informants can help clinicians distinguish people

with MCI from people with normal cognition [12]. The items related to the repetition of statements, orientation, financial management ability and visual-spatial disorientation had a high discriminatory force [12]. According to our study the majority of respondents, 92.4% (n=351), answered that their relative does not have any problems when counting the change in the store, but 18.2% (n=69) answered that their elderly close one has difficulties with paying bills and financial transactions less than half of the respondents, 40.3% (n=153) noted that their elderly close one is experiencing a problem with orientation in an unfamiliar place. Almost a quarter of the respondents, 27.1% (n=103), answered that their relative becomes more distracted outside the home, while traveling.

Lack of self-awareness of cognitive decline is a characteristic feature of dementia and people with dementia tend to deny their condition and refuse the test [14]. The detection of dementia is preferably carried out without disturbing the patient much. Surveys of informants are more suitable for this [15]. Questionnaires for informants are extremely useful for clinicians, since these tools are less affected by cognitive reserve than objective cognitive tests [16].

The using of informant-based questionnaires also helps alleviate problems related to biases in self-assessment of cognitive functions. Informants can often provide a more objective assessment of a patient's cognitive and functional status, since patients themselves may associate their deficits with age-related changes, lifestyle changes, stress and other factors. Given the new requirements for cognitive screening in the elderly, informant-based questionnaires will allow primary care physicians and other clinicians to quickly and accurately screen for cognitive decline. The using of informant-based questionnaires in the evaluation of MCI will continue to be of great importance for both clinicians and researchers, and is becoming an increasingly important component of clinical diagnosis and clinical research [17].

Conclusion

According to our investigation the most of the elderly people whose relatives (close ones) indicated of the presence of moderate cognitive disorders, only small amount of respondents indicates the absence of significant problems in the cognitive sphere and 6% respondents of elderly person showed a fairly high probability of dementia who need to seek medical help.

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Evaluation of eating disorders, kinesiophobia and dysfunctional attitudes in patients with type 2 diabetes mellitus

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Abstract

Aim: Eating disorders (EDs), dysfunctional attitudes (DAs), and limitation of movement due to kinesiophobia, which are more common in patients with type 2 diabetes mellitus (T2DM), may contribute to poor metabolic control, weight gain, disregard for treatment, and an increased prevalence of microvascular and macrovascular complications; however, current evidence is limited to small studies and restricted measures. In this study, these characteristics were assessed in patients with T2DM relative to controls, and factors independently associated with ED, DA and kinesiophobia were examined.

Material and methods: This case-control study was conducted between July 2018 and December 2018 at the Departments of Endocrinology and Psychiatry of Erzurum Regional Training and Research Hospital, Erzurum, Turkey. A total of 150 patients diagnosed with T2DM and 150 healthy controls were included. The Eating Attitudes Test (EAT), Dysfunctional Attitude Scale (DAS), and Tampa Scale for Kinesiophobia (TSK) were applied.

Results: Median age in the control group was 38 (IQR: 27 - 47) years, and 56 (IQR: 46 - 61) years in the patient group. Women comprised 67.3% of controls and 61.3% of patients. Although all scale scores were higher in the patient group compared to controls, the possible relationships were not confirmed by multiple linear regression analysis. Significant factors independently associated with higher DAS score were high age (p=0.043), high body mass index (p=0.021) and presence of comorbidity (p=0.019). Significant factors associated with higher TSK score were high age (p<0.001) and high BMI (p=0.001). High age (p<0.001) was the only parameter associated with higher EAT score. The presence of T2DM was not found to be an independent factor associated with any of the scores.

Conclusion: Our results show that, rather than the presence of T2DM, other patient characteristics were likely to be more influential on ED, DA and kinesiophobia. These show that older patients with T2DM who have comorbidities or DM-related complications are more likely to benefit from management that account for these characteristics.

Key words: type 2 diabetes mellitus, dysfunctional attitude scale, tampa scale for kinesiophobia, eating attitudes test

Introduction

Diabetes Mellitus (DM) is a metabolic disease leading to chronic hyperglycemia caused by impaired insulin secretion or response [1]. Type 2 DM (T2DM) is the most common form of the disease, and is characterized by the combination of poor insulin resistance and poor insulin secretion; whereas and Type 1 DM is caused by a definite absence of insulin secretion [2]. Glycemic control, which is the integral objective of DM management, is associated with both physical and psychological factors in patients

with T2DM [3]. It has been demonstrated that dysfunctional attitudes (DAs), eating disorders (EDs), behavioral disorders and movement disturbance are common in diabetic patients and are associated with poor metabolic control and diabetic complications [3, 4].

While the relationship between T1DM and ED is well known [5], there is little information on the relationship between T2DM and ED [4]. In a review of the literature concerning EDs in T2DM patients, the frequency of ED was shown to range between 0.3–40% [4]. In a large-scale study conducted in Germany, 663 diabetic patients were examined in terms of ED, and the current ED rate in those with T2DM was found to be 8.0% and lifetime ED rate was 14.0% [6]. Regular exercise not only delays the occurrence of T2DM but also has been shown to have possible positive effects on glycemic control. DM complications such as diabetic neuropathy, neuropathic pain and kinesiophobia affect exercise habits in patients with T2DM [7]. Kinesiophobia is defined as the anxiety against activity and physical movement resulting from the feeling of sensitivity to painful injury [8], and T2DM is known to increase the frequency of kinesiophobia [8, 9]. Finally, studies have shown that attitude-related changes and DAs can develop in individuals with chronic diseases [10], and a clear relationship between glycemic control and DA has been reported [3]. There have been studies examining the effects of these three psychophysiological factors in patients with DM; however, these studies are limited by various factors, including the number of participants, absence of controls, lack of comorbidity assessment, as well as limitations in the number or type of scales administered. As such, data on this topic is attained from limited studies without comprehensive assessments, and there is no clarity on whether DM is associated with DA, ED or kinesiophobia.

In this study, we aimed to compare patients with T2DM and controls in terms of ED, DA and kinesiophobia, and to assess whether DM and other patient characteristics were associated with scores for ED, DA and kinesiophobia.

Material and methods

Study design

This case control study was conducted between July 2018 and December 2018 at the Endocrinology and Psychiatry Departments of Erzurum Regional Training and Research Hospital, Erzurum, Turkey. The study was initiated after obtaining approval from the Ethics Committee of Erzurum Regional Training and Research Hospital (Ethics committee decision number: 37732058-514.10) and written informed consent was obtained from each of the patients and healthy controls included in the study.

Study population

A total of 150 patients diagnosed with T2DM according to World Health Organization criteria and 150 healthy controls were included in the study. Patients younger than 15 years of age and older than 70, those with neurological disease affecting cognitive functions, cases with T1DM, those with chronic obstructive pulmonary disease, thyroid dysfunction or other chronic diseases, pregnant or breastfeeding individuals, and those who refused participation were excluded from the study.

Data collection

All participants were asked to fill out a form collecting various data, including age, sex, marital status, education status, working status, smoking status, comorbidities, DM history in family, application to a dietitian, adherence to a diet, exercise, surgery history, influenza vaccination, pneumococcal vaccine, and psychiatric disease history in the patient and patient's family. Height, weight, waist circumference measurements were made and body mass index (BMI) was calculated. In addition, age at diagnosis, duration of disease, DM-related hospitalization, and drug use information were collected and recorded for the patient group. In patients, history of ketoacidosis or hyperosmolar hyperglycemic state (HHS) history, DM complications, cataract development, glaucoma presence / absence were identified from hospital records. The examined laboratory values of participants were obtained as a result of blood tests requested in routine follow-up or control examinations scheduled during the study period. All laboratory results were studied with blood samples taken from the antecubital vein after 12 hours (night) of fasting and with appropriate devices and techniques in the Biochemistry Laboratory of Erzurum Regional Training and Research Hospital.

Scales

The patients and healthy controls were asked to fill out the DAS, TSK, and EAT scales.

Dysfunctional Attitude Scale (DAS): The DAS is used to detect DAs and beliefs in individuals. The validity and reliability study for the Turkish language was performed by Şahin et al. [11]. It consists of 40 items. The items are answered with a seven-point Likert type rating, and the responses are scored as follows: 1: strongly agree, 2: agree, 3: somewhat agree, 4: neutral, 5: somewhat disagree, 6: disagree, and 7: strongly disagree. Items 2, 6, 12, 17, 24, 29, 30, 35, 37, and 40 are scored inversely. While the lowest score that can be obtained from the scale is 40, the highest score is 280 points. High scores indicate that DAs are more frequent. In addition to total score, four subdimension scores can also be calculated, and include "Perfectionism", "Need for approval", "Dependency/Autonomy" and "Inconsistency" [12].

Tampa Scale for Kinesiophobia (TSK): The most commonly used test to assess the presence of kinesiophobia is the TSK. It is a checklist comprising 17 questions [8]. The Turkish validity and reliability study of the scale was conducted by Yilmaz et al. in 2011 [13]. A 4-point Likert-type scoring method is utilized (1: strongly disagree, 4: totally agree). Items 4, 8, 12 and 16 are scored inversely and a total score is calculated. Total score ranges between 17–68 points. A high score on the scale indicates a high level of kinesiophobia [8, 14, 15].

Eating Attitudes Test (EAT-40): One of the tests used to determine eating attitudes and behaviors is the EAT-40. It was developed by Garner and Garfinkel to screen for EA [16]. In Turkey, the validity-reliability study of the test was conducted by Erol and Savaşır [17]. The EAT consists of 40 questions in total. It has a 6-point Likert-type response form (Always, Very Often, Often, Sometimes, Rarely, Never). It is a self-report scale. A cut-off point of ≥30 points is defined for the detection of Disturbed Eating Behaviors [18]. For items 1, 18, 19, 23, 27, and 39, the "sometimes" response is scored as 1 point, "rarely" as 2 points, and "never" as 3 points, while other options are evaluated as 0 points. For the other items of the scale, the "always" response is evaluated as 3 points, "very often" is evaluated as 2 points, and "often" is evaluated as 1 point, while other responses receive 0 points. Individuals scoring between 30 and 32 on EAT represent a segment of the general population who do not have any diagnosed ED symptoms but differ from the general population

in terms of eating attitudes. Those who score 33 and above have been found to demonstrate pathological eating symptoms [1, 17, 18].

Statistical Analysis

All analyses, subject to a p value threshold of 0.05 for significance, were performed on SPSS ver. 25.0. Histogram and Q-Q plots were evaluated to assess normality of distribution. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile; referred to as IQR) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Continuous variables were compared between groups with appropriate tests according to normality findings (normally distributed: independent samples t-test, non-normally distributed: Mann-Whitney U test). Categorical variables were analyzed with chi-square tests, or the Fisher's exact test where necessary. Multiple linear regression analysis (stepwise selection method) was performed to determine factors independently associated with dysfunctional attitudes, kinesiophobia and eating attitudes. All parameters demonstrating univariate differences between the control.

Results

The median age of all participants was 47 (IQR: 36-57) years; however, median age was 38 (IQR: 27 - 47) in controls and 56 (IQR: 46 - 61) years in patients. The age distribution demonstrated significant difference (p<0.001). In terms of sex, 64.3% of all participants, 67.3% in the control group and 61.3% in the patient group, were women (p=0.278). Other individual characteristics and laboratory values of all participants are depicted and compared based on the groups in Table 1 and Table 2. The summary of DM-related characteristics are shown in Table 3.

Table 1 Summary of individuals' characteristics with regard to groups

	Groups			
	Total	Control (n=150)	Type II DM (n=150)	p
Age	47 (36 - 57)	38 (27 - 47)	56 (46 - 61)	**<0.001**
Sex				
Female	193 (64.3%)	101 (67.3%)	92 (61.3%)	0.278
Male	107 (35.7%)	49 (32.7%)	58 (38.7%)	
Height	163.89 ± 9.14	165.19 ± 8.60	162.60 ± 9.51	**0.014**
Weight	77.10 ± 14.59	73.98 ± 14.88	80.22 ± 13.64	**<0.001**
Body mass index	28.86 ± 5.93	27.11 ± 5.06	30.60 ± 6.24	**<0.001**
Waist circumference	98.18 ± 12.85	93.54 ± 12.27	102.81 ± 11.73	**<0.001**
Marital status				
Married	250 (83.3%)	115 (76.7%)	135 (90.0%)	**<0.001**
Single	38 (12.7%)	35 (23.3%)	3 (2.0%)	
Divorced/Widowed	12 (4.0%)	0 (0.0%)	12 (8.0%)	
Education status				
Literate	77 (25.7%)	16 (10.7%)	61 (40.7%)	**<0.001**
Primary school	95 (31.7%)	45 (30.0%)	50 (33.3%)	
High school	53 (17.7%)	35 (23.3%)	18 (12.0%)	
University	75 (25.0%)	54 (36.0%)	21 (14.0%)	
Working status				
Working	209 (69.7%)	96 (64.0%)	113 (75.3%)	**0.033**
Not working	91 (30.3%)	54 (36.0%)	37 (24.7%)	
Smoker	43 (14.3%)	22 (14.7%)	21 (14.0%)	1.000
Comorbidities	93 (31.0%)	0 (0.0%)	93 (62.0%)	**<0.001**
Hypertension	56 (18.7%)	0 (0.0%)	56 (37.3%)	**<0.001**
Dyslipidemia	56 (18.7%)	0 (0.0%)	56 (37.3%)	**<0.001**
DM history in family				
First degree	119 (39.7%)	48 (32.0%)	71 (47.3%)	**0.007**
Second degree	154 (51.3%)	53 (35.3%)	101 (67.3%)	**<0.001**
Apply to a dietitian	116 (38.7%)	11 (7.3%)	105 (70.0%)	**<0.001**
Following a diet	61 (20.3%)	12 (8.0%)	49 (32.7%)	**<0.001**
Regular exercise	56 (18.7%)	30 (20.0%)	26 (17.3%)	0.553
Surgery history	115 (38.3%)	39 (26.0%)	76 (50.7%)	**<0.001**
Influenza vaccination	11 (3.7%)	4 (2.7%)	7 (4.7%)	0.539
Pneumococcal vaccine	2 (0.7%)	1 (0.7%)	1 (0.7%)	1.000
Psychiatric disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Psychiatric disease in family	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Table 2 Summary of laboratory measurements with regard to groups

	Groups			
	Total	Control (n=150)	Type II DM (n=150)	p
Fasting blood glucose	104.5 (93 - 146.5)	95 (87 - 102)	146.5 (113 - 224)	**<0.001**
Postprandial blood glucose	130 (99 - 208)	100.5 (90 - 121)	208 (151 - 292)	**<0.001**
HbA1c	6.1 (5.6 - 7.9)	5.6 (5.4 - 5.9)	7.9 (6.8 - 9.7)	**<0.001**
BUN	14 (11 - 17)	12.5 (10.5 - 15.5)	14.6 (11.9 - 18.5)	**<0.001**
Creatinine	0.77 (0.70 - 0.90)	0.75 (0.69 - 0.83)	0.81 (0.72 - 0.96)	**<0.001**
GFR	99 (89 - 110)	106 (97 - 117)	92 (76 - 102)	**<0.001**
ALT	18 (14 - 27)	18 (13 - 26)	20 (15 - 27)	**0.041**
AST	17 (14 - 21)	18 (14 - 21)	17 (14 - 21)	0.202
Albumin	4.36 ± 0.31	4.44 ± 0.27	4.29 ± 0.32	**<0.001**
Total cholesterol	196.27 ± 42.96	190.45 ± 35.79	202.09 ± 48.52	**0.019**
HDL	47.84 ± 11.92	50.17 ± 11.28	45.52 ± 12.12	**0.001**
Triglyceride	128.5 (79.5 - 184)	104 (68 - 159)	150 (110 - 215)	**<0.001**
LDL	121.75 ± 34.74	117.35 ± 29.92	126.14 ± 38.57	**0.028**
Sodium	138.50 ± 2.25	138.77 ± 1.74	138.23 ± 2.65	**0.040**
Potassium	4.37 ± 0.33	4.31 ± 0.30	4.43 ± 0.35	**0.002**
Calcium	9.66 ± 0.53	9.62 ± 0.46	9.70 ± 0.59	0.156
Uric acid	4.72 (3.78 - 5.77)	4.69 (3.54 - 5.59)	4.78 (4.00 - 6.03)	0.086
CRP	0.30 (0.30 - 0.52)	0.30 (0.30 - 0.39)	0.38 (0.30 - 0.74)	**<0.001**
Ketonuria	2 (0.7%)	0 (0.0%)	2 (1.3%)	0.498
Proteinuria	15 (5.0%)	0 (0.0%)	15 (10.0%)	**<0.001**
Glycosuria	50 (16.7%)	0 (0.0%)	50 (33.3%)	**<0.001**
Spot urine total protein/ creatinine	106.5 (87 - 164.5)	98 (76 - 128)	135 (100 - 248)	**<0.001**
Hemoglobin	14.21 ± 1.71	14.19 ± 1.76	14.23 ± 1.65	0.853
Hematocrit	44.13 ± 4.55	43.99 ± 4.59	44.28 ± 4.52	0.589
MCV	84.46 ± 5.38	84.42 ± 5.60	84.50 ± 5.17	0.902
Platelet (x103)	282.17 ± 72.21	278.89 ± 67.56	285.45 ± 76.67	0.432
RDW	13.1 (12.6 - 14.1)	12.95 (12.5 - 13.5)	13.3 (12.7 - 14.4)	**0.001**
PDW	12.54 ± 1.92	12.63 ± 2.03	12.44 ± 1.81	0.394
MPV	10.48 ± 0.87	10.56 ± 0.92	10.40 ± 0.80	0.114
PCT	0.29 ± 0.07	0.29 ± 0.06	0.30 ± 0.08	0.476
WBC (x103)	7.35 ± 1.93	6.95 ± 1.52	7.74 ± 2.21	**<0.001**
Neutrophil (x103)	3.94 (3.16 - 4.98)	3.83 (3.09 - 4.59)	4.16 (3.29 - 5.22)	**0.011**
Sedimentation	11 (6 - 17)	8 (4 - 13)	13 (8 - 20)	**<0.001**
TSH	1.56 (1.02 - 2.40)	1.77 (1.25 - 2.78)	1.40 (0.87 - 2.10)	**0.001**
Free T4	0.99 ± 0.14	0.98 ± 0.14	1.01 ± 0.14	0.080

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

The differences between the groups in terms of the scores of the scales were as follows: both the total DAS score (p<0.001) and all four subdimension scores were found to be significantly higher in patients compared to controls (perfectionism: p=0.001, need for approval: p<0.001, dependency/autonomy: p=0.023, inconsistency: p=0.005). Likewise, the TSK (p<0.001) and EAT (p<0.001) scores in the patient group were also significantly higher relative to the control group (Table 4).

We performed multiple linear regression analysis to determine significant factors that could predict DA, ED and kinesiophobia. We found high age (p=0.043), high BMI (p=0.021) and presence of comorbidity (p=0.019) were independently associated with higher DAS total score. Other variables included in the model, T2DM (p=0.368), sex (p=0.184), marital status (p=0.652), education status (p=0.419) and working status (p=0.301) were found to be non-significant for DAS (Table 5). We found that high age (p<0.001) and high BMI (p=0.001) were independently associated with higher TSK score. Other variables included in the model, T2DM (p=0.953), sex (p=0.314), marital status (p=0.199), education status (p=0.330), working status (p=0.119) and presence of comorbidity (p=0.434) were non-significant for TSK (Table 6). Finally, high age (p<0.001) was determined to be the only parameter associated with higher EAT score. Other variables included in the model, T2DM (p=0.274), sex (p=0.203), marital status (p=0.938), education status (p=0.205) and working status (p=0.149) were found to be non-significant for EAT (Table 7).

Table 3 Summary of diabetes mellitus-related characteristics

Age at diagnosis	47.67 ± 9.86
Duration of disease	4 (1 - 10)
Drug use	
No	0 (0.0%)
Oral antidiabetic	87 (58.0%)
Insulin	27 (18.0%)
Oral antidiabetic + Insulin	36 (24.0%)
DM-related hospitalization	
No	115 (76.7%)
1	30 (20.0%)
2	3 (2.0%)
3	1 (0.7%)
4	1 (0.7%)
Ketoacidosis/HHS coma history	5 (3.3%)
DM-related complication(s)	82 (54.7%)
Retinopathy	36 (24.0%)
Neuropathy	67 (44.7%)
Nephropathy	45 (30.0%)
Coronary artery disease	26 (17.3%)
Coronary angiography	26 (17.3%)
Coronary artery bypass graft	1 (0.7%)
Diabetic foot ulcer	7 (4.7%)
Amputation	0 (0.0%)
Cataract	29 (19.3%)
Glaucoma	5 (3.3%)

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Discussion

The relationship between the development of T2DM and environmental factors, metabolic parameters, nutritional habits and physical activity has been demonstrated by many studies [19-22]. ED, DA, and limitation of movement due to kinesiophobia, which are more common in patients with T2DM, may contribute to poor metabolic control, weight gain, disregard for treatment, and an increased prevalence of microvascular complications. The coexistence of DM and ED, DA and kinesiophobia poses a high risk in terms of morbidity and mortality [8, 12, 23]. In this study we aimed to compare the rates of ED, DA and kinesiophobia in patients with T2DM to those without DM. Despite a significant difference in age between the groups, we found that total and subdimension scores of DAS, TSK score and EAT score were significantly higher in patients with T2DM compared to controls; however, interestingly, multiple linear regression revealed that the presence of T2DM was not associated with the scores obtained from any of the tests. High age, high BMI, and presence of comorbidity were related with higher DAS total score, high age and high BMI were related with higher TSK score, and high age was the only parameter independently associated with higher EAT score.

Many studies focusing on the effects of psychological problems on diabetes reveal that psychological factors are effective on diabetes control [10, 24]. It has been seen that DA can develop in individuals with chronic diseases. A patient who has not been successful in treatment for any reason may attempt to resort to different methods, leading to non-beneficial beliefs regarding their disease and treatment. In such cases, the patient is reluctant to adhere to their main treatment [10]. A person's DAs combined with negative life events can produce automatic and involuntary negative thoughts [3, 25]. Therefore, this situation is especially important for DM patients in which long-term compliance with treatment is required. Patients should be examined in this regard and psychological support should be provided to prevent adverse events [10].

Table 4 Summary of scale scores with regard to groups

		Groups		
	Total	Control (n=150)	Type II DM (n=150)	p
Dysfunctional Attitude Scale				
Total	137.75 ± 34.40	128.89 ± 32.77	146.61 ± 33.81	**<0.001**
Perfectionism	51 (39 - 64.5)	47.5 (36 - 61)	56 (43 - 73)	**0.001**
Need for approval	37 (28 - 49)	31.5 (24 - 41)	43 (33 - 54)	**<0.001**
Dependency/Autonomy	24.12 ± 7.61	25.12 ± 8.12	23.13 ± 6.94	**0.023**
Inconsistency	20.16 ± 5.36	19.29 ± 5.70	21.03 ± 4.85	**0.005**
Tampa Scale for Kinesiophobia	36.77 ± 11.83	34.07 ± 11.27	39.47 ± 11.79	**<0.001**
Eating Attitudes Test	23 (18 - 32)	21 (16 - 28)	27 (19 - 35)	**<0.001**

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution.

In a study conducted in Beijing which evaluated DAS in 245 patients with T2DM, it was found that DA had a close relationship with HbA1C, and those with high HbA1C values had higher scores on the DAS. The authors stated that there was a significant relationship between the glycemic control of patients and findings associated with DAs [3]. In another study in which 17 T1DM and T2DM patients and 34 non-diabetic controls were included, no difference was found in terms of DAS scores between the two groups, although the incidence of depression was higher in the patient group [26]. In our study, the DAS total and subdimension scores were determined to be significantly higher in the T2DM group compared to controls. However, this possible relationship was not present in multiple linear regression analysis. High BMI, high age and the presence of comorbidity were related with higher DAS total score, suggesting that the metabolic background or underlying factors of patients were the factors that contributed to DAs. Successful management of DM largely depends on the ability of patients

to manage their disease. Studies show that individuals with DM experience various psychosocial and emotional problems that can influence DM management [24]. Considering our results showing the pronounced effect of comorbidity, age and BMI on DA, it appears that it would be beneficial to closely monitor older patients with T2DM who have comorbid diseases including metabolic syndrome.

It has been found that the increase in the frequency of T2DM in recent times is mostly associated with weight gain and decreased physical activity [19, 20]. In diabetic individuals, regular exercise has been shown to improve glucose tolerance, increase insulin sensitivity, lower HbA1C levels, and help control weight and cardiovascular risk factors [8]. The fear of movement, called kinesiophobia, is especially seen in patients with chronic pain. Patients avoid movement for the fear of suffering from pain [27]. This situation can cause more serious problems in diabetes patients, where physical activity and healthy social life are important. As the patient avoids exercise, blood sugar regulation will be more difficult, the chance of maintaining an ideal weight will decrease, and psychological discomfort will also contribute to hyperglycemia. In this respect, kinesiophobia is of great importance in the treatment and prevention of complications in patients with DM [7, 27]. In a case-control study, it was observed that individuals with T2DM had higher levels of kinesiophobia than nondiabetic participants, as determined by TSK results [8]. In the analyses of another study that included 154 patients with neuropathic pain, it was shown that diabetic neuropathy pain and fear of movement had a close relationship. It has been stated that the intensity and duration of pain and the presence of fear of falling reduce quality of life in patients with diabetic neuropathy. It was also found that pain intensity, male sex, and fear of falling were positively correlated with inactivity. As a result, it was emphasized that patients with diabetic neuropathy may have fears concerning movement, falls and pain, and that the quality of life of patients may decrease due to these fears; interestingly, the study reported no significant relationship between age and kinesiophobia [9]. In our study, we found TSK scores to be significantly higher in the T2DM group, which supports previous studies in this regard; however, regression revealed that the presence of T2DM was not a factor that increased TSK scores. It was seen that TSK scores showed a positive correlation with age and BMI. Therefore, the management approach to older T2DM patients with obesity should include evaluation of kinesiophobia, especially when painful comorbidities are present.

The development, treatment and complications of DM are closely related to diet and eating habits. The necessity of diet, the presence of a chronic process, some prohibitions and restrictions may cause anxiety in patients. For all these reasons, deterioration in eating attitudes and behaviors of patients can be observed [28]. Eds may also reduce the quality of life of patients by leading to deterioration in social functionality and physical activities [29]. There is a bidirectional relationship between ED and T2DM: such patients may have an increased risk of developing ED due to difficulties in adherence to strict diets and the presence of obesity at baseline. Secondly, since Eds evidently influence weight gain, the course and treatment of T2DM and its management may be complicated [4]. The coexistence of ED and T2DM appears to be widely variable in different studies.

In a study, the frequency of abnormal eating was found to be 40% among patients, and the logistic regression analysis of the study showed that there was a significant relationship between abnormal eating behavior and being aged <60 years [30]. In the study by Celik et al., 29.6% of patients were found to have an EAT score above 30 (i.e., had disordered eating attitudes), but there were no significant correlations between EAT scores, BMI and age [10]. In a cross-sectional study, the score obtained with the EAT-26 was found to be higher among individuals with T2DM compared to controls. In the same study, no significant difference was observed between patients with and without ED (according to EAT score) in terms of sex, age, education level, employment status, marital situation, T2DM duration, BMI, and presence of comorbidities [23]. In another cross-sectional study examining the effect of eating attitudes on the quality of life of individuals with T2DM, it was observed that 42.7% of the participants had an EAT score meeting the ≥30-point cut-off. These individuals were also found to demonstrate a higher score concerning worries about social and vocational issues as compared to those with lower scores (<30 points). In the same study, while no significant correlation was found between EAT scores and age, a significant positive correlation was found between EAT total score and BMI [1]. In a study from Turkey including 150 patients with T2DM, 26% of patients were found to have an EAT score of 30 or above. Furthermore, the authors found no significant relationship between EAT scores and sex, age, marital status, education, employment, economic standing, diabetes complications and BMI [18]. In the present study, all patients in the control group had an EAT score below 30. Although the EAT scores of T2DM patients were found to be significantly higher than the control group, regression analysis revealed that the presence of T2DM alone was not an independent factor associated with ED. High age was determined to be the only factor related with high EAT score. Although evidence from previous studies suggest that ED is associated with adverse outcomes [29] and the acute and chronic complications of diabetes [29], our regression results do not support these suggestions. Nonetheless, the significant differences between the T2DM and control groups should be mentioned, with emphasis on the fact that other underlying factors including age must be considered.

Our study has some limitations. First, the fact that it was a single-center study limited the generalizability of the results. Second, the differences in age, sociodemographic characteristics and laboratory results between the patient and control groups may have affected the results. In order to obtain clearer results, multicenter studies with larger patient counts and homogenous distribution of characteristics among groups are required.

In conclusion, although the data we obtained showed that DA, ED and kinesiophobia were more common in T2DM patients than in controls, these univariate relationships were not confirmed by regression analysis. In addition, it was observed that the probability of the occurrence of all three disorders increased with age. Furthermore, high BMI increased the frequency of DA and kinesiophobia, and DA was more common in those with comorbidities. For successful T2DM management, in addition to appropriate medical treatment, supportive approaches for nutrition, physical activity and mental support are required in particularly older patients with comorbidities and higher BMI.

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Serum vitamin D levels in high-risk HPV infected patients, is there any relation?

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Abstract

Objective: Human Papilloma Virus (HPV) is a sexually transmittable virus and is the main etiologic cause of uterine cervical cancers. Beyond that, vitamin D is a steroid structured lipid-soluble vitamin, enhancing both humoral and cellular immune responses. In our study, we aimed to investigate the relationship between vitamin D levels and high-risk HPV infections.

Material and methods: A total of 143 patients who applied to the gynecology outpatient clinic between June 2020 and August 2020 were included in the study. Patients with high-risk HPV positivity constituted the study group, and HPV-negative patients constituted the control group. Serum vitamin D levels were compared between the groups.

Results: The mean vitamin D level of all patients included in the study, HPV(+) and HPV(-) patients were 17.57±8.73, 17.54±9.20 and 17.63±7.83, respectively. In the study group 10.2% of the patients and in the control group 8.5% had adequate vitamin D levels. No significant differences in vitamin D levels and in terms of distribution according to categorical vitamin D level have been observed between the groups (p=0.774, p=0.989).

Conclusion: Vitamin D levels were comparable between HPV positive and HPV negative groups, but study and controls both had very low sufficient vitamin D levels. In Turkey and especially in our region (Zonguldak), vitamin D deficiency is almost endemic, and this might be the main reason that both of the groups have very similar vitamin D measurements.

Key words: human papillomavirus, vitamin D, cervix uteri

Introduction

Cervical cancer is the 3rd most common cancer among women all around the world [1]. In economically disadvantaged regions, where cervical cancer screening and prevention programs cannot be financed well, cervix cancer remains the main reason for cancer morbidity and mortality.

Human Papilloma Virüs (HPV) is the most common sexually transmitted disease in adults [2]. Most of the HPV infections were cleared rapidly by natural immunity; however, it may become permanent and cause cancer in some cases [3]. A healthy and stable cellular immunity plays a major role in the eradication of HPV infection of the uterine cervix. HPV is the almost single cause of cervix cancer and is present in 99.7% of cases. Among all high-risk types, HPV 16 is responsible for 50% of the cases, while HPV 18 is present in 20 percent. Other high-risk (HR) types as HPV 31, 33, 45, 52 ve 58 are the cause of the remaining 19 percent [4,5]. HPV positivity was seen in 3.5% in Turkey. The commonest HPV genotypes were 16, followed by 51,

31, 52 and 18 [6]. Cervical cancer estimated age-standardized incidence is 4.8/100.00 and cumulative risk of incidence is %0.78 for Turkey [7].

Vitamin D is considered by many experts as a hormone, lipid-soluble and is in steroid structure and causes many different effects in various tissues [8,9]. Vitamin D plays an important role in immunocompetence. Vitamin D must be in sufficient levels to keep an immune system to prevent any disease, and its deficiency leads to severe disease mortality and morbidity. There is a defined inverse proportionality with vitamin D levels and prolonged upper and lower respiratory tract infections [10]. Studies evaluating cervical-vaginal infections and vitamin D deficiency state that lower vitamin D levels are associated with bacterial vaginosis and chlamydia [11,12].

Vitamin D facilitates the immune modulation of T and B lymphocytes and plays a major role in the natural immune system by proofing them to differentiate in the adaptive immune system, helping monocytes become macrophages, and enhancing their capacity for phagocytosis [13]. Natural immunity is strongly associated with the capacity of producing AMP. AMP, in fact, facilitates the phagocytic cells to react for the infected area and enhances the immune response by regulating the cells responsible for cellular reactions, leading inactivation in pathogens [14]. Vitamin D locally is related to the production of endogen antimicrobial peptides (AMP). In addition, vitamin D helps form a physical barrier, remodeling the proteins of the tight junctions, gap junctions, and adhere junctions to form an extra resistance against bacteria & viruses in the genitourinary system, respiratory system, and the skin [15].

In venereal diseases as HPV, first reaction in the vagina and uterine cervix plays a major role in facing the pathogen in the first place. If the viral capacity could be immunologically beaten off in the first interaction, HPV infection could not persist and could not cause the cervical changes. As mentioned earlier, AMP present in the vagina and cervix plays a major role [16]. An intact barrier is also essential to prevent the transmission of HPV. The proliferation and differentiation process of keratinocytes is regulated by vitamin D. In keeping and maintaining an intact epidermal barrier in the skin, vaginal mucosa, and genitourinary system vitamin D plays a protective and efficient role [17].

So in our study, we wanted to evaluate if the deficiency or the main levels of vitamin D may play a role in the infections with high-risk HPV-subtypes.

Materials and Methods

This study was approved by the ethics committee for clinical studies with the approval number of 2020/12 of Zonguldak Bulent Ecevit University, Turkey. Before the study began, all human participants gave informed consent for HPV testing and for inclusion in the present study. Patients examined in Gynecological Clinic of Zonguldak Bulent Ecevit University between June 2020 - August 2020 has been included to the study. Patients with a positive high-risk screening test have been added to the study group, and other patients with a negative HPV test without cervical complaints formed the controls. Patients' HPV test results and cervical smear screening test results are obtained from the national cervical cancer screening program. In Turkey, women aged between 30 and 65 years are invited for HPV based screening by primary level health staff (family physicians and so called KETEM screening centers) every five years. All screening processes are free of charge. The sample for HPV testing was taken with a brush and put into 5 ml of Standard Transport Medium, HPV DNA specimen collection kits (Qiagen HC2) for HPV DNA analysis. For women who are HPV positive by Hybrid Capture2 (Qiagen), genotyping is performed with the CLART kit (Genomica) [6].

Patients using vitamin D supplementation, with a metabolic disease, liver and kidney disease, or any systemic illness that might affect the vitamin D metabolism and pregnant women are excluded from the study.

A 3ml peripheral venous blood sample was taken from each participant under sterile conditions for the assessment of serum 25-hydroxyvitamin D. Blood samples were collected in labeled tubes and then centrifuged, and the separated sera were stored at -20◦C.

We categorized serum 25-hydroxyvitamin D levels according to prior clinical conventions, as follows: <12 ng/mL, indicative of severe vitamin D deficiency; 12–19 ng/mL, indicative of vitamin D deficiency; 20–29 ng/mL, indicative of vitamin D insufficiency; and ≥30 ng/mL, indicative of vitamin D sufficiency [18].

Statistical analysis of the study was performed using the R 4.0.3 package program. The descriptive statistics of the quantitative variables in the study are given with their mean, standard deviation, median, minimum and maximum values; qualitative variables are reported as frequency and percentage. The conformity of quantitative variables to normal distribution was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare two groups of quantitative variables that did not show normal distribution. Chi-Square Test was used to compare between HPV positive and negative groups according to the categorical distribution of vitamin D. Results less than p=0.05 in all statistical analyses were considered statistically significant.

Results

One hundred forty-three patients fulfilling the admission criteria have been added to the study; among those, 94 HPV negative patients formed the control group, and 49 high-risk HPV positive patients concluded the study group. Patients were between 18-65 ages, and the mean age was 42.54±10.13. Seven of the study group were HPV 16 positive, 33 were HPV other high-risk positive, 6 patients were HPV 16, and HPV other high-risk positive, 2 of them HPV 18 and HPV other high-risk positive and finally 1 patient was HPV 16, HPV 18 and HPV other high-risk positive (Table 1). Considering the cervical smear results, 77 cases had benign results as atrophic cells or infection, 6 patients had Atypical Squamous Cells of Undetermined Significance (ASCUS), 1 had Low-Grade Squamous Intraepithelial Lesions (LSIL) (Table 1).

Table 1 HPV and smear results of patients

	n
HPV Subtypes	
HPV 16	7
HPV Other	33
HPV 16+HPV Other	6
HPV18+HPV Other	2
HPV 16+HPV18+HPV Other	1
Smear Results	
Benign Results (atrophic cells or infection)	77
ASCUS*	6
LSIL*	1

*ASCUS: Atypical Squamous Cells of Undetermined Significance, LSIL: Low-Grade Squamous Intraepithelial Lesions

Table 2 Vitamin D levels of control and study groups

	Mean	Median	Std. Deviation	Minimum	Maximum
HPV+	17.63	16.03	7.83	4.88	35.58
HPV -	17.54	16.34	9.20	3.59	55.02

p=0.774 (Mann-Whitney U test)

Table 3 Distribution of groups according to categorical vitamin D level

	Categorical Vitamin D Level*			
	Severe deficiency	Deficiency	Insufficiency	Sufficiency
HPV-	28 (%29.8)	35 (%37.2)	23 (%24.5)	8 (%8.5)
HPV+	14 (%28.6)	8 (%36.7)	12 (%24.5)	5 (%10.2)

p=0.989 (Chi-Square Test)
*: <12 ng/mL, indicative of severe vitamin D deficiency; 12–19 ng/mL, indicative of vitamin D deficiency; 20–29 ng/mL, indicative of vitamin D insufficiency; and ≥30 ng/mL, indicative of vitamin D sufficiency

The mean vitamin D level of all patients included in the study was 17.57±8.73. When comparing the mean vitamin D levels of controls and study (17.54±9.20 vs. 17.63±7.83, respectfully), there was no statistically significant difference (p=0.774) (Table 2). 28.6% of the study cases had severe vitamin D deficiency, 36.7% were deficient, while 24.5% had insufficient levels of vitamin D. Only 10.2% of the study group had sufficient levels of vitamin D. Similarly, controls had very comparable levels; 29.8% severe deficient, 37.2% deficient, 24.5% insufficient and 8.5% sufficient. No significant difference has been observed between the groups in terms of distribution according to categorical vitamin D level. (p=0.989) (Table 3).

Discussion

Vitamin D plays an active role in the immune system. HPV is eliminated by the immune system. Clearing this agent from the cervix and the factors affecting it are important. Because if it cannot be removed, it can cause cervical precancerous lesions and cancer. Therefore, the relationship between HPV and vitamin D levels is important. In our study, we compared vitamin D levels in HPV positive and HPV negative patient groups. No significant differences in vitamin D levels and in terms of distribution according to categorical vitamin D level have been observed between the groups in our study.

Recent studies brought more interest in the relationship between vitamin D and cancer. Vitamin D and its metabolites' antiangiogenetic effect and its effect on cell proliferation, apoptosis, cell differentiation promote scientific curiosity to this level [19]. Vitamin D and its receptor are considered to play a major role in the pathogenesis of gynecological malignancies. Studies have shown cervical cancer incidence and mortality are inversely correlated with vitamin D levels, and increasing the serum vitamin D helps preventing the risk of cervical neoplasia [20-22]. In a randomized controlled trial, patients with Cervical Intraepithelial Neoplasia grade 1 (CIN1) receiving vitamin D for six months vs. placebo had higher remission rates [23]. Özgü et al., in their research defining the relation between HPV infection/ cervical intraepithelial neoplasia and vitamin D deficiency, pointed out that the HPV DNA-positive group had lower vitamin D levels than healthy controls. The same study concluded that considering the effects of vitamin D on the immune system, its deficiency might be related to HPV persistence and may cause cervical intraepithelial neoplasia [19]. In studies with CIN and vitamin D, Vahedpoor et al. found that the use of vitamin D was effective in mild CIN regression, Schulte-Uebbing et al. demonstrated that vaginal vitamin D supplements had an antidysplastic effect on mild CIN but not on moderate CIN [24,25].

There are few studies evaluating the relation of vitamin D and HPV infection. In a study, patients with venereal warts (condyloma acuminatum) have been associated with lower vitamin D levels [26] but besides that, there are also studies that do not detect a difference [27]. In another research, vitamin D deficiency has been found related with both low-risk HPV infection (1.41; 95% CI 1.23 to 1.61; p<0.001) and high-risk HPV infection (1.25; 95% CI 1.04 to 1.49; p=0.014) [28].

Shim et al., examined 2353 sexually active women in their original research and pointed that cervical-vaginal HPV prevalence is associated with less-than-optimal levels of serum vitamin D. They also calculated per each 10 ng/mL decrease in serum 25(OH)D level the odds of high-risk HPV infection were increased (adjusted odds ratio [aOR], 1.14; 95% confidence interval [CI], 1.02–1.27) [18]. In the Chu at all study, they found a correlation between low vitamin D levels and higher abnormal smear and HPV positivity [29].On the other hand, in another controlled trial, 404 women between ages 30-50 did not have a correlation with lower serum 25(OH)D levels and high-risk HPV infections [16]. In the study in which serum 25-hydroxyvitamin D level and vaginal HPV prevalence, incidence and clearance were evaluated, no relationship was found between vitamin D level and HPV prevalence and incidence, but a modest negative correlation was found in HPV clearance [30]. In the study, evaluated associations between vitamin D biomarkers and persistent high-risk human papillomavirus (hrHPV) detection, among mid-adult women evaluated monthly for 6 months, serum concentrations of 25(OH)D were positively associated with a short-term pattern of persistently detected hrHPV. But associations were inconsistent and significant only in sensitivity analyses [31].

Vitamin D deficiency is an important public health problem, and unfortunately, it is also very common in Turkey. In major studies it has been found that in general population 74,9%, in women in reproductive age 54% was found vitamin D deficient [32,33]. Due to the fact that Turkey is a huge country with various microclimates, vitamin D levels show a huge variability changing in the region. Habitations as İzmir, with moderate weather and more sun exposure vitamin D deficiency, might become as low as 27.8%. In other areas with insufficient sunlight exposure, it may rise to 76.3%-83.4% [26,34]. Studies evaluating vitamin D deficiency have shown that it is very common in our -Zonguldak- region [35,36].

All cases included in our study had mean vitamin D levels of 17.57±8.73. When we look at the mean serum vitamin D levels of controls (17.54±9.20) and study (17.63±7.83), no significant difference has been observed (p=0.774). Spite the fact that we planned our study for the summer period to avoid lower levels of vitamin D, only 10,2% in HPV positive and 8,5% of HPV negative groups had sufficient levels of serum vitamin D. In a similar study from Turkey, Mertoglu et al. did not found any relation concerning vitamin D deficiency and HPV infection, but they too have very few sufficient patients in study and controls (Vitamin D deficiency 82.4% in HPV positive group and 83.4% in HPV negative group). Both groups had a severe deficiency in our study population concerning vitamin D. This might directly affect our results and other Turkish-made studies designed on this topic [26]. More extensive population-based studies, based on vitamin D sufficient and insufficient groups and their HPV

screening results, may improve the current knowledge on this topic.

Our study had some limitations. The main limitation of this study was the smaller sample size. The data were collected from a single center. As in previous observational studies, we measured vitamin D levels only at baseline. We used only one vitamin D biomarker (25-hydroxyvitamin D).

Turkey/Zonguldak province, where we performed our study, has endemic low vitamin D levels due to climate factors (less sun exposure), nutritional and clothing habits. We did not find differences in serum vitamin D levels in HPV positive and HPV negative groups, but this may be influenced by the high ratio of vitamin D deficient patients.

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The effect of anesthesia management on mortality and morbidity in patients who underwent transcatheter aortic valve implantation

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Abstract

Objectives: We aimed at investigating the effects of two different anesthesia techniques in our patients who underwent transcatheter aortic valve implantation (TAVI).

Material and methods: The effects of two different anesthetic methods were retrospectively evaluated in 100 patients who underwent TAVI between January 2010 and October 2020. Patients were divided into a general anesthesia (GA) group and a sedation-local anesthesia (S-LA) group according to the anesthetic methods used.

Results: Of 100 patients who underwent transcatheter aortic valve implantation, 20 (20%) received GA, and 80 (80%) received S-LA. The mean ages of the patient groups undergoing GA and S-LA were 76.20±7.22 and 75±8.44 years, respectively. The duration of the procedure and anesthesia was significantly longer in the GA patient group than in the S-LA patient group. With the exception of the logistic European Society of Cardiac Operative Risk Assessment, the demographic and preoperative data of the two groups were similar. The most common comorbidity in both groups was hypertension. When comparing complications between groups, the incidence of intraoperative hemodynamic instability, ephedrine use, inotropic drug use, intra-aortic balloon pump placement, postoperative infection and cardiac tamponade was significantly higher in the GA group. The length of intensive care and hospital stay was similar between the groups, but the 30-day and 3-month mortality rates were significantly higher in the GA group than in the S-LA group.

Conclusion: S-LA provided more stable hemodynamics, shorter operative and anesthetic times, fewer intraoperative and postoperative complications, and reduced mortality. S-LA application during the TAVI procedure is a more reliable alternative to GA.

Key words: general anesthesia, sedation, aortic valve stenosis, transcatheter aortic valve implantation

Introduction

Aortic stenosis (AS) is the most common heart valve pathology in developed countries. Its prevalence is reported to increase with age, reaching 9.8% between 80 and 89 years of age [1-3]. Left untreated, symptomatic AS has a poor prognosis and leads to increased mortality [4,5]. Transcatheter aortic valve implantation (TAVI) is an interventional treatment modality that provides a non-surgical replacement of the aortic valve [6]. With increasing worldwide attention, this new technology has revolutionized the treatment of AS. Although many studies have demonstrated the effectiveness of TAVI in AS, there is no consensus on the most appropriate type of anesthesia to support TAVI [7]. While TAVI was originally performed under general anesthesia (GA), technological advances in catheters and other devices, and the increasing experience of anesthesiologists and surgeons, allowed TAVI to be performed under sedation-local anesthesia (S-LA) [8,9]. In our study, we aimed to investigate retrospectively the application examines the success of two different anesthetic methods, their impact on complications, and 1-, 3-, and 6-month mortality rates in patients undergoing TAVI.

Material and methods

Local Ethics Committee approval (2011-KAEK-25 2020/10-16) was obtained for this study, which was conducted to evaluate patients who underwent TAVI between January 2010 and October 2020. The study was conducted in accordance with the principles of the Helsinki Declaration and included patients over 18 years of age undergoing TAVI under GA or S-LA. Patients who had pre-procedure cardiac arrest required open-heart surgery during and after TAVI, and patients under 18 years of age with missing data were excluded from the study. Data were collected retrospectively from patient charts, hospital automation systems, and anesthesia follow-up charts. The patients were divided into two groups GA and S-LA groups according to the anesthetic method used. Patient demographics, comorbidities, American Society of Anesthesiologists (ASA) Physical Status Classification, European Society of Cardiac Operative Risk Assessment (EuroSCORE) or Society of Thoracic Surgeons (STS) scores, ejection fraction (EF), anesthesia method, anesthesia and operative time, type of aortic valve used, site of catheterization, hemodynamic data, need for inotropic drugs, length of ıntensive care unite (ICU) and hospital stay, the incidence of complications, and mortality rates were recorded. Data on 1-, 3-, and 6-month mortality rates were obtained from hospital records, telephone contacts, and civil registration offices. Since all data were collected retrospectively and managed anonymously, patient consent was not required.

At our hospital, the TAVI procedure is approved by a committee consisting of a cardiologist, a cardiac surgeon, and an anesthetist. The severity of aortic stenosis is determined by transthoracic echocardiography. In the preoperative anesthesia assessment, detailed medical history, comorbidity, physical examination, laboratory and consultation results, ASA, logistics EuroSCORE and STS score results are evaluated.

The TAVI procedure is performed in our hospital's angiography unit under sterile conditions and accompanied by fluoroscopy. The type of anesthesia to be performed is decided based on the evaluation of the GA or S-LA, the general condition of the patient, and the details of the procedure. For GA applications, the anesthetic agent may change. Generally, midazolam, fentanyl, propofol and ketamine hydrochloride in induction; Rocuronium is also preferred as a muscle relaxant. Sedation is with fentanyl and midazolam. An intraoperative reduction in systolic blood pressure greater than 25% from baseline or less than 90 mmHg was considered hypotension. Fluid therapy is used for low blood pressure. If there is no response, infusions of ephedrine, norepinephrine, and dobutamine are scheduled according to the patient's hemodynamic status. The transfemoral approach is preferred in most patients. Subclavian/axillary, transaortic, and transapical approaches are alternative approaches in patients unsuitable for the transfemoral approach. The most common valves are the Edwards family (Edwards Lifesciences, Irvine, USA), the Medtronic family (Medtronic, Minnesota, USA), and the Portico valve (St. Jude Medical Inc., USA). At the end of the procedure, all patients are transferred to the ICU.

Statistical analysis

The statistical analyses of the study were carried out using the SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Data with and without normal distribution were presented with, respectively, the mean ± standard deviation and the median (25-75%). Categorical variables were presented with numbers and percentages. For group comparisons, and frequency comparisons in categorical variables the chi-square test were used. The independent sampling test was used for comparing the mean values of the continuous variables. The nonparametric Mann-Whitney test was used for comparison of the median values. A p-value of <0.05 was accepted for statistical significance.

Results

The data of a total of 115 TAVI patients were analyzed. Two patients who had cardiac arrest, 2 patients who underwent cardiac surgery during the procedure, and 11 patients with incomplete mortality data were excluded from the study. S-LA (n=80) ve GA (n=20) patients who underwent the TAVI procedure were evaluated for the anesthesia methods. The clinical and demographic data of the patients before and during the procedure are presented in Table 1.

Table 1 Patients' demographic features.

Variable	Group 1 (n=80)	Group 2 (n=20)	P
Age, years	76,5(71-82)	75(73-82)	0,841
Gender, n (%)			
Female	39(48,8)	9(45,0)	0,764
ASA, n (%)			
III	60(75,0)	12(60,0)	0,181
IV	20(25,0)	8(40,0)	0,181
Smoking, n (%)	25(31,3)	8(40,0)	0,457
EF,(mean±SD)	47,16±11,95	41,25±16,61	0,072
Disease diagnosıs, n (%)			
Aortic stenosis	53(66,3)	27(33,8)	0,916
Aortic stenosis-CAD	13(65,0)	7(35,0)	0,916
Logistic EuroSCORE,(mean±SD)	23,21±11,04	30,00±19,93	0,043
STS risk score,(mean±SD)	6,71±6,18	5,21±3,79	0,303
Operation duration, min	95,68±22,17	116,26±24,48	<0,001
Total anesthesia time, min	107,12±22,95	134,75±33,96	<0,001
Valve type, n (%)			
Edwars-Sapien valve	22(27,5)	7(35,0)	0,509
Medtronic-core valve	37(46,3)	8(40,0)	0,615
Portico St. Jude valve	21(26,3)	5(25,0)	0,909
TAVI route, n(%)			
Right transfemoral	63(78,8)	19(95,0)	0,091
Left transfemoral	15(18,8)	1(5,0)	0,134
Right subclavian	1(1,3)	0(0,0)	0,615
Left Subclavian	1(1,3)	0(0,0)	0,615
Length of stay in the ICU (days)	1(1-2)	4(3-5)	0,092
Length of stay in hospital (days)	2(1-3)	4(2-9)	0,854
30-day mortality	4(5,0)	5(25,0)	0,005
3-month mortality	8(10,0)	6(30,0)	0,021
6-month mortality	16(20,0)	7(35,0)	0,154

The results are expressed as: median (25-75), mean and standard deviation (SD), number (n) and percent (%).
Chi-square Test, Mann-Whitney U Test,

The median age of the patients was 76 (48-94) years. The patients did not differ significantly with respect to age, gender, ASA, EF, and the STS score. In the GA group, the mean Logistic EuroSCORE (30.00±19.93), duration of the operation (116.26±24.48 min.) and duration of anesthesia (134.75±33.96 min.) were significantly higher (p=0.043, p<0.001 and p<0.001,

Table 2 Distribution of comorbidities and laboratory by groups

Variable	Group 1 n=80	Group 2 n=20	P
Comorbidity n (%)			
HT	61(76,3)	11(55,0)	0,058
DM	30(37,5)	9(45,0)	0,539
COPD	8(10,0)	5(25,0)	0,074
CVD	5(6,3)	0(0,0)	0,251
Kidney diseases	5(6,3)	1(5,0)	0,833
Coronary artery disease	33(41,3)	8(40,0)	0,919
Heart failure	7(8,8)	3(15,0)	0,405
Hemogram			
Preoperative	11,12±2,13	11,92±2,49	0,154
Postoperative	10,26±2,67	10,02±4,08	0,747
Hematocrit			
Preoperative	33,18±5,53	34,43±6,44	0,384
Postoperative	31,04±7,45	29,97±11,22	0,607
BUN			
Preoperative	28,01±13,53	21,40±10,92	**0,046**
Postoperative	28,08±14,87	21,15±13,01	0,060
Creatine			
Preoperative	1,18±0,43	1,12±0,48	0,570
Postoperative	1,12±0,44	0,92±0,51	0,098

The results are expressed as: mean and standard deviation (SD), number (n) and percent (%).
HT: Hypertantion, **DM:**Diabetes Mellitus, **COPD:**Chronic Obstructive Pulmoner Disease, **CVD:**Cerebrovacular disease, **BUN:** Blood Urea Nitrogen

Table 3 Comparison of intra and postoperative complications of the groups

	Group 1	Group 2	P
İntraoperative, n (%)			
Hemodynamic instability	7(8,8)	10(50,0)	**<0,001**
Ephedrine use	6(7,5)	9(45,0)	**<0,001**
Use of inotropic drugs	4(5,0)	9(45,0)	**<0,001**
NTG use	1(1,3)	0(0,0)	0,615
Temporary pacemaker application	79(98,8)	19(95,0)	0,284
Permanent pacemaker application	10(12,5)	4(20,0)	0,387
IABP insertion	0(0,0)	2(10,0)	**0,004**
Postoperative, n (%)			
Bleeding	1(1,3)	1(1,3)	0,284
Paravalvular leak	1(1,3)	0(0,0)	0,615
Neurological dysfunction	2(2,5)	1(5,0)	0,558
İnfection	0(0,0)	1(5,0)	0,044
Process site infection	3(3,8)	1(5,0)	0,799
Process site hematoma	7(8,8)	2(10,0)	0,861
Procedure site pseudoaneurysm	3(3,8)	1(5,0)	0,799
Renal dysfunction	1(1,3)	0(0,0)	0,615
Myocardial infarction	3(3,8)	2(10,0)	0,251
Cardiac tamponade	0(0,0)	2(10,0)	**0,004**

The results are expressed as: number (n) and percent (%).
NTG: Nitroglycerin, IABP: İntraaortic Balloon Pump

respectively). In both the GA and the S-LA groups the right femoral approach and the Medtronic valve were used most frequently. The groups did not differ significantly in terms of ICU and hospital stay but the 30-day and 3-month mortality rates were significantly higher in the GA group of patients (p=0.005 and p=0.021, respectively). The preoperative and postoperative laboratory investigation results and comorbidities of the two groups are shown in Table 2. The preoperative blood urea nitrogen (BUN) was significantly higher (p=0.046) in the SA group. The most frequently found comorbidity was hypertension in both groups. The intraoperative and postoperative recorded complications of the S-LA and GA groups of patients are compared in Table 3. The results on intraoperative hemodynamic instability, ephedrine use, inotropic medication use and intra aortic balloon pump (IABP) fitting, postoperative infection, and cardiac tamponade were significantly higher in the GA group of patients (p<0.001, p<0.001, p<0.001, p=0.004, p=0.044 ve p=0.004, respectively).

Discussion

In our study, in which we retrospectively analyzed the data of patients who underwent TAVI with the diagnosis of severe AS, according to the anesthesia method; in the GA group, the mean logistic EuroSCORE was significantly higher, and the operation and anesthesia times were significantly longer. There was no difference between the groups in intensive care and hospital stay, but the 30-day and 3-month mortality rates were found to be significantly higher in the GA group than in the S-LA group.

Severe AS is a common degenerative valve disease in the elderly patient group with a high incidence of mortality. TAVI, which has been applied as a noninvasive method in patients with high surgical risk in recent years, has become an alternative to surgical aortic valve replacement [10]. In the PARTNER study (Placement of aortic transcatheter valves, multi-center study) [11], it was stated that the procedure is an effective and safe treatment. In TAVI procedures, anesthesia applications vary depending on the experience of the team, the patient's systemic comorbidities, and the approach techniques are chosen for valve implantation [11,12]. Various anesthesia methods such as GA, S-LA, or regional anesthesia have been defined for TAVI applications [13]. In our study, S-LA was preferred in 80 (80.00%) of 100 patients and GA was preferred in 20 (20.00%) patients (Table 1).

Büyükçoban et al. [14] and Çakıer et al. [15] reported the mean age of patients who underwent TAVI as 78.25±8.24 and 78.19±6.90, respectively. In our study, the mean age was 75.99±7.83 years and was consistent with the literature. Comorbidities such as advanced age are also important in increasing the surgical risk score and determining the type of anesthesia to be administered to patients. Although there was no difference between the groups in our study, hypertension was the most common comorbidity. This result was similar to many studies [14,15].

Preoperative surgical risk assessment in patients with severe AS is made according to Logistic EuroSCORE and STS risk scoring. While there was no difference between STS scores in our patients, the logistic EuroSCORE value was significantly higher in GA patients than in S-LA patients (30.00±19.9, 23.21±11.04, p=0.04, respectively). In many studies, it has been stated that GA with a high EuroSCORE value increases the risk of mortality and therefore S-LA should be preferred [16]. In our study, 30-day and 3-month mortality rates were found to be high in GA patients and this result was consistent with the literature. However, there are studies indicating that GA facilitates the management of hemodynamic instability in patients with a high EuroSCORE value and is an appropriate anesthesia method to enable the surgical team to work more comfortably [17]. On the other hand, technological developments and the increasing experience and experience of the team have brought S-LA applications to the fore in TAVI patients. In the literature, it has been stated that the transfemoral approach is a factor in the choice of anesthesia [17]. In our study, the transfemoral approach was used in 97.6 % of S-LA patients. While the TAVI procedure is preferred over surgery in high-risk patients because of its less invasiveness, it is stated that performing anesthesia with S-LA instead of GA may be beneficial for the patient [18]. Many

studies have reported that patients who underwent GA showed longer processing times compared to the LA group [11,12]. In this study, the duration of the procedure and the anesthesia of the patients in the GA group were significantly longer than in the S-LA group.

In general, patients before TAVI may be hypovolemic due to diuretic and vasodilator treatments that can be applied, and the cardiac depressant effects of anesthetic drugs used in GA may cause hemodynamic instability [19]. For these reasons, some publications have noted that the use of vasopressors and inotropic agents is more common during GA [19,20]. According to the results of our study, intraoperative hemodynamic instability, ephedrine use, and inotropic drug use were highest in the GA group.

Some complications that may occur during and after the TAVI procedure have been reported in the literatüre [15,21]. Villablanca et al. [21] stated that there was no difference in complications such as cardiovascular mortality, stroke, permanent pacemaker requirement, vascular complications, and annular rupture in GA and S-LA applications in TAVI procedure. Cakier et al. [15] compared anesthesia methods in TAVI procedure and found no difference in terms of complications such as minor vascular complications, sepsis, pneumonia, acute renal failure, infection, and cerebrovascular disease. However, they reported that it was higher in the group that underwent GA due to complications such as sudden rupture of the procedure and cardiac tamponade. In our patients, postoperative cardiac tamponade and infection were found to be significantly higher in the GA group with IABP insertion during the TAVI procedure.

There are many studies in the literature that have evaluated ICU and hospital lengths of stay and 30-day mortality after anesthesia management for TAVI procedures [21-23]. In these studies, it was stated that S-LA significantly shortened the length of stay in the ICU and hospital, and the 30-day mortality rate was lower than GA. In a few studies, no difference was found in the 30-day mortality rate in the comparison of GA and S-LA in the TAVI procedure [24,25]. In our study, in contrast to the literature, no difference was found between the groups in terms of ICU and hospital length of stay and 6-month mortality, while 30-day and 3-month mortality rates were significantly lower in the S-LA group. The low number of patients undergoing GA may be the reason why we could not find a difference in ICU and hospital stays.

Our study had several limitations. This study was single-center, retrospective, and had a relatively small sample size. The other limitation is that the group of patients in S-LA is much larger than the group in GA. In terms of the effect of the anesthesia method on mortality and complications, there is a need for further studies with an equal or higher number of patients. Another limitation is that cost-effectiveness was not included in the study. However, we think sharing experiences with 100 patients is also important to contribute to the literature.

Conclusion

We compared the effects of two different anesthesia techniques in 100 patients who underwent transcatheter valve implantation. We found more stable hemodynamics, shorter operative and anesthetic times a reduced number of intraoperative and postoperative complications with reduced mortality in patients that underwent S-LA. S-LA application during the TAVI procedure is a more reliable alternative to GA.

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Anxiety, depression, and other related factors in Turkish pregnant women during the COVID-19 pandemic's first wave: A cross-sectional and web-based study

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Abstract

Aim: This research aims to determine attitudes, behaviors, anxiety and depression levels of pregnant women regarding the prevention measures from the COVID-19 pandemic.

Material and methods: The cross-sectional study population consists of pregnant women (N=1008) in Turkey. Data were collected with Information Form, Hospital Anxiety and Depression Scale.

Results: Anxiety score was 8 and above in 63.6% of the pregnant women while that of depression was 8 and above in 52.1% of them. There was an increase in risk of anxiety in pregnant women regarding the items about family and loved ones being infected by COVID-19 2.36 times, and about the baby being infected and lost 2.61 times. This rate increased 1.60 times in those who could not have screening tests due to pandemic, and 1.40 in those whose frequency of attending antenatal controls decreased. Risk of depression, on the other side, increased 1.59 times in those who were anxious about not receiving any companion support at birth, 1.65 times in those who couldn't have screening tests due to the pandemic, 1.38 times in those who didn't plan the place to give birth and didn't learn its conditions, and 1.55 times whose frequency of attending antenatal controls decreased.

Conclusion: It has been determined that psychosocial support services and antenatal care may be regarded as fundamental fields of intervention.

Key words: COVID-19 pandemic, anxiety, depression, pregnancy

Introduction

Spreading of COVID-19 infection throughout the whole world since December 2019 was followed by a declaration of pandemic on March 11, 2020. Upsetting consequences such as a rapid spread of the virus associated with this infection, mortality, healthcare and uncertainty in economic processes have affected the whole world. People were physically isolated from their families, friends, and society, and businesses and schools around the world were closed [1]. During the pandemic process, the risk of illness and death due to infection on one side, and psychological and social consequences of changing living conditions with radical measures taken to protect from contamination such as social isolation and quarantine on the other side have affected mental health [2]. During the pandemic, pregnant women have emerged as a particularly vulnerable and disadvantaged group. Pregnant women experience anxiety and fear for the health of both themselves and their baby, and for their families during this period [1, 3]. Together with an increased risk of serious complications, being vulnerable to infections caused by natural suppression of the immune system during pregnancy [4], risk of vertical transmission of infections, insufficient information about treatment of the disease and uncertainties are important concerns for

pregnant women [5]. Italian pregnant women have been reported to experience a high rate of anxiety related to vertical transmission [6]. With an effect of hormonal changes during pregnancy, incidence of anxiety disorder varies between 1.3-8.5% and the incidence of depression between 5-15% [7 –9]. In addition to the increased anxiety risk and depression during pregnancy, psychosocial effects increase even more with the pandemic [10]. A research conducted in China, reported that during the pandemic period, pregnant women had significantly high depression and anxiety symptoms [5]. During the pandemic process, obligatory behavioral changes such as social isolation, remote working, transportation difficulties, child care are emerging as well as increasing concerns about the health of pregnant women, their families in general and their unborn babies [11]. In addition, the pandemic is boosting prenatal anxiety. Therefore, special support is needed for pregnant women during the pandemic [12]. In the first wave of the COVID-19 pandemic, infection treatment has been mainly focused on [13 – 15], and thus there is limited information on mental state and psychological needs [1, 5, 12]. In the literature, approximately one out of every four pregnant women are reported to experience clinically high depression symptoms and one out of every three pregnant women to experience anxiety in COVID-19 pandemic [10]. In order to prevent negative health outcomes resulting from the COVID-19 pandemic, information is also needed to determine the current mental states of pregnant women and to conduct intervention researches and to develop strategies. Therefore this research aims to determine the anxiety and depression levels of pregnant women in the COVID-19 pandemic.

Some additional factors (socio-demographic characteristics, obstetric characteristics, antenatal follow-up, pregnancy-related concerns, coping behaviors, etc.) related to the anxiety and depression levels of pregnant women during the COVID-19 pandemic were also examined.

Research Questions (RQ):

RQ (1) In what level is the prevalence of anxiety and depression in pregnant women in the COVID-19 pandemic?

RQ (2) Are there a relationship between the anxiety and depression levels of pregnant women and some socio-demographic variables during the COVID-19 pandemic?

RQ (3) Are there a relationship between the anxiety and depression levels of pregnant women and some obstetric variables during the COVID-19 pandemic?

RQ (4) Are there a relationship between anxiety and depression levels of pregnant women and antenatal follow-up characteristics during the COVID-19 pandemic?

RQ (5) Are there a relationship between the anxiety and depression levels of pregnant women and their concerns about pregnancy during the COVID-19 pandemic?

RQ (6) Are there a relationship between the levels of anxiety and depression in protective and coping behaviors of pregnant women during the COVID-19 pandemic?

Material and methods

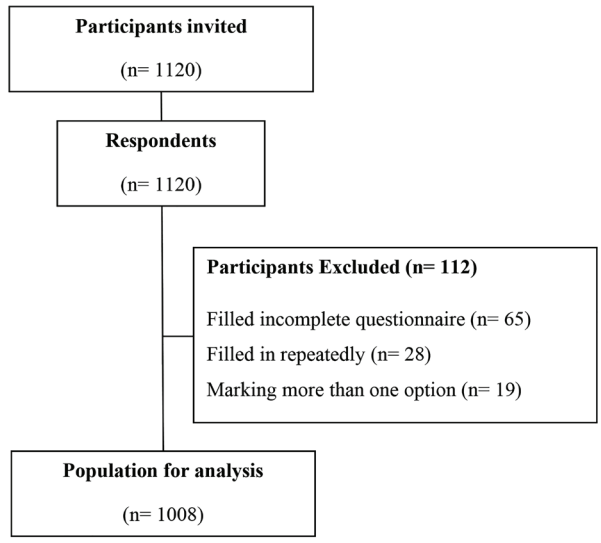
Study design

The research was designed as a cross-sectional study. The study was conducted online between May 1 and June 22 in 2020, during the initial spreading of the COVID-19 pandemic. Data were collected using online Google forms on social media (Facebook, Instagram and Whatsapp group) on pregnancy, childbirth, midwifery, reproductive health, and antenatal education themed groups.

Study population

The research population in Turkey live births in 2020 (N=1.112.859) was reported [16]. As a cross-sectional and web-based study, this research aimed to have a sample size of at least 385 individuals (1% absolute deviation, 50% unknown prevalence, and 95% confidence level). OpenEpi Version (2013) was used to create this sample size [17]. Participants of the research included a total of 1120 pregnant women. One hundred and twelve questionnaires were excluded because they were not filled out completely (n=65) and more than one option was marked (n=19) and they were filled in repeatedly (n=28). The study sample decreased to 1008 pregnant women as data entry repetitions and underfilled forms were excluded from the assessment (Figure 1).

Figure 1 - Flow-chart of study population



The inclusion criteria were as follows: having at least a primary school education, being pregnant, not having any diagnosed psychiatric disorder, not using psychotropic medicine, agreement to participate in the questionnaire. Being not pregnant, non-volunteering, not completing all the questions of the survey were the criteria for exclusion.

Data collection

The questionnaire had two main parts. The first main part consisted of an Information Form developed by researchers according the literature [5, 7, 9], this form consisted of three sub sections, which were; i) introductory characteristics of pregnant women (age, education level, occupation, region of residence, income status, individuals living together at home, child for care or individuals over 65 years old, etc.), ii) pregnancy-related characteristics (pregnancy history, gestational week, risky situations during pregnancy, pregnancy follow-up frequency, consulting for anxiety/concerns, etc.), iii) COVID-19 infection protection measures, attitudes and behaviors (perceiving behavioral responses to COVID-19 infection and behavioral situations, etc.). Third sub section (iii) of an Information Form consisted of 10 items for evaluating COVID-19 infection protection measures, attitudes and behaviors about pregnancy. This section had questions related to keeping social distance, washing hands, avoiding public transport, nutrition, exercising, sleeping, etc. Six of the items were related to the evaluation of prevention measures and attitude, and in this evaluation, pregnant women were asked to mark the appropriate one among the "I believe", "I am undecided" and "I don't believe" categories. Four

items were related to coping behaviors and pregnant women were asked to mark how often they performed these behaviors as "frequently", "sometimes", or "never". After development, this third section was also evaluated for clarity by two experts in the field of women's health. Since this study was conducted in the first wave of the pandemic, the standard COVID-19 infection protection measures, attitudes and behaviors evaluation form could not be reached.

The second sub section was Hospital Anxiety and Depression Scale [18]. The scale was adapted to Turkish by Aydemir et al. [19]. The scale is used to evaluate the individual's risk in terms of anxiety and depression. It is in likert type (0,1,2,3), seven items of it are for anxiety subscale (1.,3.,5.,7.,9.,11. and 13.) and seven items are for (2.,4.,6.,8.,10.,12. and 14.) depression subscale. The lowest scale score participants can get is 0 and that of the highest is 21. According to the cut-off value of the scale, the pregnant women having anxiety and depression scores ≤8 were classified as having "normal" in this research. Additionally, scale scores between 8-10 were classified as "borderline abnormal" and scores between 11-21 were classified as "abnormal". In the original research of the scale, the Cronbach's alpha for the anxiety subscale was 0.85, and the depression subscale was 0.80 [18]. In the Turkish version of the research, the Cronbach's alpha for anxiety and depression scales is 0.85 and 0.77, respectively [19] with slight difference. These values were found to be 0.84 and 0.75, respectively in our research.

Data analysis

Data were analyzed with Statistical Package for the Social Sciences 22.0 software. Likelihood of the data in showing normal distribution was evaluated through Shapiro–Wilk tests of normality. In this sense, non-parametric tests were used for the analysis since the data did not show normal distribution. Data analysis were used for distributions of means (standard deviations), numbers (percentages), Mann Whitney U, Kruskal Wallis H and, Bonferroni-corrected. Additionally, in order to identify factors that affect the risks of depression and anxiety, logistic regression analysis was performed. In the so-called analysis, the enter method was applied and odds ratio (OR) values were presented in a 95% confidence interval (95% CI). The p value of the analysis indicating <0.05 was considered as results being statistically significant.

Ethical Considerations

This research was conducted in full compliance to the Helsinki Declaration principles. The consent form was on the first page of the online survey. Confidentiality of all information to be provided was assured to the participants. Participation in the research required the consent form in the first page to be filled, which asked for voluntary agreement to participate in the research. A pregnant woman could fill out the questionnaire after declaring her consent to participate voluntarily. Ethical consent for the research was granted by Ethics Committee of a state university (30.04.2020- E.14660). Approval of the Ministry of Health was obtained by electronic submission (2020-06-09T01_48_33.xml).

Results

The mean age of pregnant women was 27.63±4.35. Mean number of pregnancies in women was 1.53±0.86, mean number of living children was 0.65±0.77, and the mean of gestational week was 24.86±9.09. Of the pregnant women living in seven geographical regions of Turkey, 35.3% were in Marmara, 24.1% in Central Anatolia and 40.6% in other regions (Aegean: 14.9%, Mediterranean: 9%, Black Sea: 7%, Southeast Anatolia: 6.6%, Eastern Anatolia: 3%). 61.4% reside in the city center, 99.5% of the pregnant women were married in our research. Education levels was found 52.9% university graduate, and 55.6% of them expressing that their income was equal to expenses. During the COVID-19 pandemic; 50.9% of them stated that their income status decreased. Approximately half of the pregnant women were housewives, 24% of them have worked online at home during the COVID-19 pandemic, and 10.6% of them could not work for various reasons (such as dismissal, unpaid leave), during the pandemic.

Anxiety mean score of the pregnant women was 9.25±4.28, and the mean depression score was 7.77±3.88. Depression scores of the pregnant women were found as 47.9% of them being 7 points and below, 28.1% between 8-10 points, 24% 11 points and above. Anxiety scores were found as 36.4% of the pregnant women having 7 points or less, 26.8% having 8-10 points and 36.8% having 11 points or above. Anxiety mean scores of women with postgraduate education were lower than the other groups ($p<0.05$). In pregnant women whose income was less than their expenses, the mean scores of anxiety and depression were significantly higher ($p<0.05$). Considering the employment status of pregnant women, it was observed that the anxiety score means of those who went to work every day, those who were dismissed or those who compulsorily took unpaid leave are significantly higher than the other groups ($p<0.05$). The depression score means of the pregnant women in terms of employment status also indicated that the so-called mean score was less compared to other groups in the ones who went to work a few days in a month ($p<0.05$). Conversely, the depression score mean was significantly higher in the group whose spouses were dismissed during the COVID-19 pandemic than the ones who worked online at home ($p<0.05$). Anxiety score mean was higher in pregnant women who stated that their income decreased at the pandemic period ($p<0.05$). However, the depression score mean was significantly lower compared to other groups in the one who stated that their income didn't change during the pandemic ($p<0.05$). Additionally, the depression score means were significantly higher compared to other groups in the one whose members were in their first trimester. When the anxiety and depression levels of pregnant women were examined according to the change before and after June 1, 2020, when the normalization in social life started; While the anxiety score means of the pregnant women participating in the research on 01.06.2020 and after were higher than before 01.06.2020 ($p<0.05$), it was found that the depression score means showed similarity ($p>0.05$) (Table 1).

The anxiety and depression mean scores were significantly higher in those whose frequency of going to antenatal follow-ups decreased, those who did not have screening tests during the pandemic, who did not learn the place and conditions of birth, and those who needed psychological support due to the anxiety and worries experienced during the pandemic ($p<0.05$) (Table 2). Anxiety and depression levels of pregnant women were examined according to some of their concerns during the COVID-19 pandemic and according to this; scale score means were significantly higher in those who are worried about their family/loved ones affected by it, those who were worried about the long duration of the pandemic, those who were worried about being infected when referring to the health institution for pregnancy follow-up, those who were worried about being infected while having birth, who are worried about the transmission of COVID-19 infection to their baby, those who

Table 1 Distribution of anxiety and depression scores according to some sociodemographic and obstetric characteristics of pregnant women

Socio-demographic variables	n	Anxiety		Depression	
		Mean±SD	Analysis*	Mean±SD	Analysis*
Residing place					
Provincial city centre	619	9.10±4.35	0.182	7.62±3.97	0.296
District centre	324	9.56±4.13		8.04±3.74	
Town/Village centre	65	9.03±4		7.77±3.84	
Educational status					
Primary[1]	123	9.20±4.03	**0.0001**[a] **4-1 4-2 4-3**	8.01±3.43	0.068
High school[2]	262	10.04±4.03		8.23±3.80	
University[3]	533	9.13±4.38		7.58±4.04	
Post-graduate[4]	90	7.71±4.27		7.22±3.70	
Income					
Income less than expenses[1]	181	10.56±4.54	**0.001**[b] **1-2 1-3**	8.86±4.06	**0.0001**[b] **1-2 1-3**
Income and expenses equal[2]	560	9.21±4.15		7.52±3.72	
Income more than expenses [3]	267	8.43±4.17		7.54±3.99	
Employment during COVID-19 pandemic					
Online working at home[1]	242	8.60±4.18	**0.0001**[c] **2-1 2-3 2-5 4-1 4-3 4-5**	7.58±3.83	**0.006**[d] **3-1 3-2 3-4 3-5**
Going to work everyday[2]	49	11.22±4.41		8.96±4.29	
Going to work a few days a month[3]	57	8.91±4.36		6.77±4.23	
Dismissed + Unpaid leave[4]	107	10.29±4.70		8.70±3.83	
Housewife[5]	553	9.19±4.14		7.66±3.81	
Employment of spouse during COVID-19 pandemic					
Online working at home [1]	140	8.86±4.16	0.053	7.06±3.90	**0.007**[e] **4-1**
Going to work everyday [2]	465	9.59±4.29		7.95±3.93	
Going to work a few days a month[3]	240	8.73±4.11		7.49±3.75	
Dismissed + Unpaid leave [4]	70	8.81±4.84		8.05±4.20	
Unemployed[5]	93	8.91±4.21		7.66±3.50	
Changes in income during COVID-19 pandemic					
Had no change[1]	489	8.67±4.08	**0.0001**[f] **2-1 2-3**	7.27±3.90	**0.0001**[g] **1-2 1-3**
Yes, income decreased[2]	511	9.80±4.38		8.22±3.79	
Yes, income increased+Other[3]	8	8.88±5.17		9.13±5.82	
Changes in social life					
Pregnant women before June 1, 2020	766	9.09±4.22	**0.027** [h]	7.63±3.75	0.059
Pregnant women on June 1 and later	242	9.74±4.42		8.19±4.27	
Gestational week					
First trimester[1]	143	9.74±4.41	0.119	8.73±3.94	**0.002**[i] **1-2 1-3**
Second trimester[2]	413	8.92±4.08		7.78±3.75	
Third trimester[3]	452	9.39±4.40		7.45±3.95	
Number of pregnancies					
Primiparous	645	9.21±4.45	0.459	7.70±3.92	0.359
Multiparuos	363	9.31±3.96		7.89±3.82	

**Mann-Whitney U test was used in paired groups. In more than two groups, Bonferoni corrected Kruskall-Wallis H test was used and post hoc analysis was examined with Mann-Whitney U test.*

[a]*Significantly lower in the ones who said "Post-graduate".*

[b]*Significantly higher in the ones who said "Income less than expenses".*

[c]*Significantly higher in the ones who said "Going to work everyday" and "Dismissed or Unpaid leave".*

[d]*Significantly lower in the ones who said "Going to work a few days a month".*

[e]*Significantly higher in the ones who said "Dismissed or Unpaid leave".*

[f]*Significantly higher in the ones who said "Yes, income decreased".*

[g]*Significantly lower in the ones who said "Had no change".*

[h]*Significantly lower in the ones who said "Pregnant women before June 1, 2020"*

[i]*Significantly higher in the ones who said "First trimester".*

Table 2 Distribution of anxiety and depression scores of pregnant women according to antenatal follow-up

Antenatal Follow-up Information	n	Anxiety		Depression	
		Mean±SD	Analysis*	Mean±SD	Analysis*
Going to follow-ups decreased before the delivery					
Yes	664	9.65±4.17	**0.0001**[a]	8.11±3.79	**0.0001**[a]
No	344	8.47±4.39		7.10±3.98	
Having consultancy on the phone					
Yes	474	9.37±3.98	0.163	7.64±3.67	0.453
No	534	9.13±4.53		7.88±4.07	
Going to a private physician in this process, not to a hospital.					
Yes	389	9.39±4.37	0.451	7.99±3.93	0.169
No	619	9.15±4.22		7.63±3.86	
Couldn't have screening test done because of this process					
Yes	242	10.23±4.17	**0.0001**[a]	8.77±3.82	**0.0001**[a]
No	766	8.94±4.27		7.45±3.86	
Have you planned the place where you will have delivery and learned the conditions?					
Yes	508	8.94±4.13	**0.042**[b]	7.17±3.73	**0.0001**[b]
No	500	9.55±4.41		8.37±3.96	
Do you think you need information and psychological support for your anxieties/concerns during this process?					
Yes	372	11.19±4.11	**0.0001**[a]	9.25±3.91	**0.0001**[a]
No	636	8.11±3.95		6.90±3.60	

**Mann-Whitney U test was used.*
[a]Significantly lower in the ones who said "No".
[b]Significantly lower in the ones who said "Yes".

Table 3 Distribution of anxiety and depression scores according to pregnancy-related concerns

Some Concerns Experienced by Pregnant Women	n	Anxiety		Depression	
		Mean±SD	Analysis*	Mean±SD	Analysis*
I'm worried that it might affect my family, my loved ones.					
Yes	947	9.45±4.23	**0.0001**[a]	7.86±3.89	**0.0001**[a]
No	61	6.15±3.90		6.31±3.55	
I'm worried that the psndemic will continue for a long time.					
Yes	953	9.39±4.26	**0.0001**[a]	7.84±3.89	**0.021**[a]
No	55	6.71±3.80		6.56±3.62	
I'm worried about being infected when referring to the health facility for pregnancy follow-up					
Yes	883	9.54±4.23	**0.0001**[a]	7.96±3.87	**0.0001**[a]
No	125	7.14±4.02		6.38±3.70	
I'm worried about being infected while having delivery.					
Yes	840	9.78±4.17	**0.0001**[a]	8.07±3.88	**0.0001**[a]
No	168	6.60±3.78		6.24±3.57	
I'm worried that COVID-19 will be transmitted to my baby while having delivery.					
Yes	908	9.58±4.24	**0.0001**[a]	7.93±3.911	**0.0001**[a]
No	100	6.22±3.338		6.29±3.36	
I'm worried about infecting and losing my baby.					
Yes	813	9.89±4.19	**0.0001**[a]	8.12±3.92	**0.0001**[a]
No	195	6.55±3.55		6.31±3.38	
I'm worried that I won't have companion support at delivery.					
Yes	807	9.72±4.27	**0.0001**[a]	8.11±3.89	**0.0001**[a]
No	201	7.35±3.78		6.38±3.55	
I'm worried about not being able to breastfeed my baby after delivery.					
Yes	719	10.05±4.14	**0.0001**[a]	8.32±3.83	**0.0001**[a]
No	289	7.25±3.97		6.40±3.69	

**Mann-Whitney U test was used.*
[a]Significantly lower in the ones who said "No".

Table 4 Distribution of anxiety and depression scores by prevention and some coping behaviors from the COVID-19 pandemic

Characteristics regarding prevention and coping behaviors	n	Anxiety		Depression	
		Mean±SD	Analysis*	Mean±SD	Analysis*
Characteristics regarding prevention					
Social activities and reducing the number of people interviewed will reduce the risk of catching COVID-19 infection;					
I believe[1]	935	9.13±4.19	0.061	7.66±3.89	**0.017[a] 3-1 3-2**
I'm undecided[2]	50	10.14±4.2		8.66±3.95	
I don't believe[3]	23	11.87±6.48		10.22±5.13	
Not using public transport/reducing the use of public transport will reduce the risk of catching COVID-19 infection;					
I believe[1]	938	9.17±4.22	0.278	7.65±3.84	**0.005[a] 3-1 3-2**
I'm undecided[2]	45	9.82±4.08		8.67±3.66	
I don't believe[3]	25	11.00±6.08		10.36±4.90	
Not being in shopping areas / markets / shops will reduce the risk of catching COVID-19 infection;					
I believe[1]	919	9.17±4.22	0.346	7.65±3.83	**0.019[a] 3-1 3-2**
I'm undecided[2]	53	9.77±4.22		8.58±3.61	
I don't believe[3]	36	10.44±5.64		9.56±5.04	
Cleaning or disinfecting hard surfaces like door handles, table, chair, etc. will reduce the risk of catching COVID-19 infection;					
I believe[1]	897	9.19±4.24	0.376	7.67±3.87	0.072
I'm undecided[2]	84	9.81±4.30		8.45±3.71	
I don't believe[3]	27	9.26±5.26		8.81±4.64	
Washing my hands regularly with soap and water will reduce the risk of catching COVID-19 infection;					
I believe[1]	941	9.20±4.24	0.651	7.70±3.86	0.116
I'm undecided[2]	49	9.61±4.27		8.39±3.81	
I don't believe[3]	18	10.72±6.10		9.72±4.81	
Maintaining social distance will reduce the risk of catching COVID-19 infection;					
I believe[1]	933	9.14±4.21	0.095	7.64±3.82	**0.002[a] 3-1 3-2**
I'm undecided[2]	53	10.38±4.50		8.77±3.99	
I don't believe[3]	22	10.86±5.89		10.77±3.98	
Characteristics regarding coping behaviors					
I prayed/meditated					
Frequently[1]	776	9.56±4.28	**0.0001[b] 3-1 3-2**	7.91±3.87	0.161
Sometimes[2]	133	8.70±3.98		7.26±3.87	
Never[3]	99	7.52±4.23		7.35±4.02	
I paid attention to my diet					
Frequently[1]	890	9.20±4.26	0.534	7.58±3.86	**0.0001[d] 1-2 1-3**
Sometimes[2]	91	9.48±4.30		9.18±3.67	
Never[3]	27	9.85±4.80		9.11±4.25	
I slept regularly					
Frequently[1]	714	8.91±4.18	**0.0001[c] 3-1 3-2**	7.36±3.80	**0.0001[c] 3-1 3-2**
Sometimes[2]	203	9.71±4.12		8.28±3.50	
Never[3]	91	10.87±4.90		9.78±4.63	
I slept regularly					
Frequently[1]	345	8.99±4.18	0.479	6.94±3.75	**0.0001[c] 3-1 3-2**
Sometimes[2]	318	9.33±4.13		7.82±3.67	
Never[3]	315	9.43±4.54		8.61±4.08	

** Checked with Bonferoni corrected Kruskall-Wallis H test, Mann-Whitney U test in post Hoc analyses.*

[a]Significantly higher in the ones who said "I don't believe".

[b]Significantly lower in the ones who said "Never".

[c]Significantly higher in the ones who said "Never".

[d]Significantly lower in the ones who said "Frequently".

Table 5 Evaluation of factors affecting anxiety and depression levels with regression analysis

Variables (Reference cagetory)	Anxiety		
	p	OR	95% CI
Lower- Upper			
The frequency of going to antenatal control decreased (yes)	**0.029**	1.401	(1.035-1.897)
I couldn't get the screening tests done because of this process (yes)	**0.004**	1.609	(1.169-2.214)
I'm worried that the disease will infect me while I'm having delivery (yes)	**0.045**	1.665	(1.012-2.741)
I'm worried that I won't be able to breastfeed my baby after delivery (yes)	**0.001**	1.811	(1.267-2.587)
I'm worried about infecting and losing my baby (yes)	**0.000**	2.618	(1.587-4.317)
I'm worried that it might affect my family, my loved ones (yes)	**0.026**	2.365	(1.109-5.042)
Variables (Reference cagetory)	**Depression**		
	p	OR	95% CI
Lower- Upper			
The frequency of going to antenatal control decreased (yes)	**0.003**	1.552	(1.166-2.066)
I couldn't get the screening tests done because of this process (yes)	**0.002**	1.659	(1.200-2.292)
Have you planned the place where you will have delivery and learned its conditions? (no)	**0.016**	1.388	(1.060-1.810)
I'm worried that I won't have companion support at delivery (yes)	**0.009**	1.591	(1.120-2.259)
I'm worried about not being able to breastfeed my baby after delivery (yes)	**0.008**	1.557	(1.124-2.156)
I'm worried about infecting and losing my baby (yes)	**0.025**	1.541	(1.057-2.249)
Trimester (first trimester)	**0.040**	1.222	(1.009-1.481)

were worried about the loss of their baby after birth, those who were worried about the lack of companion support, those who were worried about not being able to breastfeed their baby after birth ($p<0.05$) (Table 3).

The scale scores of pregnant women regarding their perceptions on protection recommendations of international and national health organizations during the COVID-19 pandemic indicated that the mean depression scores are significantly higher in those who do not believe that reducing the number of social events and meetings, not using or limited use of public transport, avoiding from places such as shopping venues, maintaining social distance will reduce the risk of COVID-19 infection ($p<0.05$), when compared to ones who were of the opposite opinion and who were undecided on this matter. Anxiety and depression levels of pregnant women according to some coping behaviors in the COVID-19 pandemic were also examined and this revealed that the anxiety score means of pregnant women who prayed/meditated frequently was significantly higher than the other groups ($p<0.05$). The mean depression score in pregnant women who paid attention to their nutrition was significantly lower than the other groups ($p<0.05$). In pregnant women who answered "never" to "I slept regularly" behavior, the mean scores of anxiety and depression were significantly higher than those who answered "sometimes" and "often" ($p<0.05$). The mean depression score of pregnant women who answered "never" to the behavior "I exercised regularly at home" was significantly higher than those who answered "sometimes" and "often" ($p<0.05$) (Table 4).

Multivariate logistic regression analysis indicated that six factors were significant in the development of anxiety. Level of this anxiety was 2.61 times in those who were worried about their babies getting infected and dying (95% CI: 1.587-4.317; p=0.000), 2.36 times in those who were worried that their family members and loved ones may be affected by COVID-19 (95% CI: 1.109-5.042; p=0.026), 1.81 times in those who were worried about not being able to breastfeed their baby after birth (95% CI: 1.267-2.587; p=0.001), 1.66 times in those who were worried about the transmission of COVID-19 infection at giving birth (95% CI: 1.012-2.741;p=0.045), 1.60 times in those who could not have the screening tests due to the pandemic (95% CI: 1.169-2.214; p=0.004), and 1.40 times in those whose frequency of going to antenatal control decreased (95% CI: 1.035-1.897; p=0.029) .

According to multivariate logistic regression analysis, seven factors were found significant in the development of depression. The fact that the pregnant women were not able to have screening tests because of the pandemic increased the probability of depression 1.65 times (95% CI:1.200-2.292; p=0.002), frequency of going to antenatal controls 1.55 times (95% CI:1.166-2.066; p=0.003), anxiety of not having a companion support at the birth 1.59 times (95% CI:1.120-2.259; p=0.009), inability to plan the place to give birth and not learn the conditions (95% CI:1,060 -1.810; p=0.016), worrying about not being able to breastfeed after birth 1.55 times (95% CI:1.124-2.156;p=0.008), worrying that their baby will be infected and losing their babies 1.54 times (95% CI: 1.057-2.249; p=0.025), and being in the first trimester 1.22 times (95% CI: 1.009-1.481; p=0.040) (Table 5).

Discussion

Stress, depression and anxiety disorders experienced during pregnancy are reported to have negative effects on the psychosocial development of the baby [20]. COVID-19 pandemic which affect the whole world, in all areas of life, may be a risk-increasing situation in terms of maternal mental health. In this context, assessment of pregnant women will contribute to the measures to be taken and the care to be given [21]. This research suggests that the attitudes and behaviors of pregnant women regarding pandemic protection measures and their anxiety and depression levels. Depression score was found above the scale cut-off values in the 52.1% of pregnant women and anxiety score in 63.6% of them, and thus risk of experiencing mental problems seem to be high. A cross-sectional research conducted before the COVID-19 pandemic indicated that while the probability of depression increased (10.0%) in late pregnancy, anxiety symptoms decreased (14.2%) [22]. Similarly, Dikmen-Yildiz et al. (2017) in our country, reported the prevalence of depression as 14.6% and of anxiety as 29.6% in pregnancy [23]. In addition, anxiety and depression levels were found to be significantly higher than research conducted in pregnant groups before the pandemic [24, 25]. A high anxiety level [10, 26] and depression [26] is reported in researches conducted during the COVID-19 pandemic process in pregnant women. In a multicenter cross-sectional research comparing the mental states of pregnant women prior to and after the

declaration of COVID-19 outbreak in China, it is reported that the pregnant women who were evaluated after the declaration of the COVID-19 outbreak showed significantly higher anxiety levels and a higher rate of depression symptoms [5]. A research conducted with pregnant women in Canada also reported that the risk of anxiety and depression symptoms are high [1]. Limited research conducted during the current pandemic report anxiety rates between 63-68% during pregnancy [11]. Similarity of the literature and our research findings showed that pregnant women were under threat against anxiety and depression risks. This research has found that lower education levels, lower income levels, full-time work and compulsory unpaid leave increase the risks of anxiety and depression. While the risk of depression in the first trimester was higher in pregnant women whose income decreased during the pandemic process, depression score was lower in those whose income level did not change. The depression scores of pregnant women whose spouses were dismissed and whose spouses had to take unpaid leave in this pandemic process were higher than those whose spouses work online at home. Another research found the risk of depression and anxiety is high in primiparous pregnant women who are in low socioeconomic status and work full time [5]. The high anxiety and depression scores of women with low socioeconomic levels may be explained by the economic fluctuation and increased unemployment anxiety caused by the COVID-19 pandemic crisis [21]. The necessity to go to work full-time is seen as a worrying result as it carries the risk of socialization and contact during the pandemic process. Risks of anxiety and depression are high in those whose frequency of antenatal care during the pandemic period decreased, those who did not have screening tests, those who did not know the place and conditions of birth, and those who need psychological support due to pandemic concerns.

The pandemic's impact on the world in a short time, limited information about the transmission routes, the effects of the pandemic on pregnancy, and the uncertainty of vertical transmission are among the important concerns for the pregnant women [3, 5]. It is recommended to pay attention to quarantine measures taken in the pandemic globally and not to go to health institutions unless necessary [28]. However, the need to go to health institutions for the tests and controls that pregnant women should have can cause dilemma and anxiety [29]. Community alerts and messages appear to create global concern among individuals and lead to self-censorship in hospitals in terms of contamination risk [25, 29]. The epidemic raises concerns about childbirth in many aspects, including disrupted expectations for antenatal care in pregnant women. Decrease in the frequency of receiving antenatal care during COVID-19 pandemic process, not having screening tests, not knowing under which conditions to have delivery and needing psychological support, and the high risk of anxiety and depression are important findings.

Many authorities state that it will be appropriate to reduce the frequency of antenatal care in health institutions in order to minimize the human density and virus transmission risk in health institutions and that this care can be carried out with technological support. However, antenatal care and follow-up, which cannot be provided directly in the health institution, are recommended to be carried out on various social media platforms such as Skype, Zoom. Health and government actors should be aware of high stress levels during pregnancy in the pandemic and guidance should be provided to support pregnant women [31]. Similarly, Peahl et al. (2020) recommend reducing the frequency of direct antenatal care and follow-ups, and using services that integrate telehealth practices as an alternative [32]. Health authorities and policymakers work together to minimize the risk of infection and virus spread in the fight against the COVID-19 pandemic in the world and in Turkey [26]. Lockdown and quarantine have been applied in some areas after detecting the first cases in Turkey and strict measures have been taken to comply with social distance rules throughout the country. When the number of cases decreased over time, changes such as the removing of the lockdowns and the opening of closed shopping centers after June 1, 2020 were made. Anxiety scores of pregnant women who took part in the research after this date are higher than that of the ones before this date. The mobility that has emerged with the change in social life rules is thought to cause the increase in anxiety along with the increasing of the risk of contamination in this research. Pregnant women have a high risk of anxiety and depression if they are worried about COVID-19 pandemic affecting their families, the long duration of the pandemic, the infection of themselves and their baby during antenatal follow-up and delivery, lack of accompanying support at birth, not being able to breastfeed their baby after birth. The possibility of clinical depression symptoms increases the anxiety of the pregnant woman and her baby about COVID-19 infection transmission [1]. The sources of concern frequently reported to obstetricians in a research conducted in India are hospital visits for antenatal services and ultrasonography scans, infection protection measures, concern about social media messages and infant health and breastfeeding [33]. Concerns about pregnancy, fetus/baby and health services can also cause mental problems during the pandemic process. Those who do not believe that social activities and limiting the number of people interviewed, not using or limited use of public transport, not being in environments such as shopping malls, and attempts to maintain social distance will reduce the risk of COVID-19 infection are at higher risk of depression. The idea that protection from contamination will not be possible is thought to lead to a high risk of depression in these pregnant women. Individuals put into effect self protection measures against threats without realizing it, and they cannot perceive public service ads and messages sent to protect themselves from infection. In this respect, anxiety, which can lead to more serious mental problems, is a factor that should not be ignored for mental well-being [34]. In this context, providing information that creates trust is thought to be more be beneficial. Anxiety risk was found to be higher in pregnant women who frequently prayed/meditated during the pandemic process. Additionally, the risk of depression is high in pregnant women who often do not pay attention to their diet and do not exercise regularly at home. The risk of anxiety and depression is higher in those who have irregular sleep. A research emphasizes that increased social support and exercise have a protective role in reducing anxiety and depression during the pandemic process [1]. While the pandemic process is a global concern that may trigger the risk of anxiety and depression during pregnancy, the psychological changes experienced in this process also affect physical activity, nutrition and sleep problems.

Limitations

This study has two limitations. First is that we did not use a previously validated questionnaire for data collection on COVID-19 infection protection measures, attitudes and behaviors of pregnant women. The second is that the research has been conducted online on social media platforms. Pregnant women who do not use social media platforms are not included in the study. Therefore, the results of the study cannot be generalized to all pregnant women.

Conclusion

The study findings indicate that COVID-19 pandemic and its vital effects may pose a risk on the mental health of pregnant women. Perinatal mental health interventions should be one of the priority areas during an epidemic. Safe and applicable strategies should be established during the pandemic to manage perinatal mental health under the conditions of psychological helplines and tele-health counseling.

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Pulse dose glucocorticosteroid therapy in COVID-19 pneumonia patients in an intensive care unit

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Abstract

Introduction: Coronavirus pneumonia occurs with severe lung tissue damage and rapid activation of cytokines and chemokines, called "cytokine storm," and simultaneously with a high risk of thrombosis and thromboembolism. There is no specific therapy for new coronavirus infection (COVID-19) also for cytokine storm. Therefore it is necessary to search for effective anti-inflammatory treatment. The aim of this study is to investigate the efficacy of pulse-dose glucocorticosteroid use in the treatment of COVID-19 patients hospitalized in the intensive care unit.

Material and methods: The efficacy of pulse dose glucocorticosteroid therapy with 250-1000 mg for three days methylprednisolone 1 mg/kg for 5-7 days more in 144 patients in an intensive care unit with severe coronavirus pneumonia was studied in a retrospective analysis of 55 patients in the standard dose glucocorticosteroid (1 mg/kg/day methylprednisolone) group. The study's primary endpoint was mortality in ICU, and the secondary endpoint was the effects on inflammatory markers. The treatment groups' disease severities were initially the same.

Results: Pulse dose glucocorticosteroid therapy did not reduce overall intensive care mortality but also increased it. C-reactive protein and fibrinogen levels decreased statistically significantly from the 1st day of admission, but D-dimer did not change statistically significantly. Neutrophilia was seen after steroid use, but it was significantly higher in the pulse dose group. Recovery in the pulse dose group was slower (median ICU stay was 12 days in the pulse dose group versus 10 days in the standard dose group, p=0.002)

Conclusion: Pulse dose glucocorticosteroid therapy has a rapid anti-inflammatory effect but did not reduce intensive care mortality, also increased intensive care length of stay in our cohort.

Key words: pulse dose glucocorticosteroids, critical care, mortality, thrombosis, D-dimer, COVID-19

Introduction

Severe forms of corona virus disease 2019 (COVID-19) are accompanied by viral pneumonia with total damage of small pulmonary vessels, bronchioles and alveoli. Progressive systemic inflammation plays a significant role in the pathogenesis of COVID-19. Pathological immune system hyperreactivity, manifested by uncontrolled cytokine activation of immune cells and release of cytokines and chemokines by the latter, was called "cytokine storm" [1]. Cytokine storm increases the risk of acute respiratory distress syndrome and can lead to multiple organ failure. Thus, reducing systemic inflammatory response activity is one of the urgent problems of treatment of patients with COVID-19 since this process triggers pathophysiological mechanisms of the coagulation cascade and lung damage [2].

Research on the management of patients with COVID-19 related cytokine storm phenomena prioritizes immunosuppressive preamplifiers from monoclonal antibody groups. IL-6 blockers (tocilizumab and sarilumab) and IL-1 inhibitors (anakinra) are recommended for cytokine storm treatment in severe COVID-19 [3]. The recommendations of the Ministry of Health of the Republic of Turkey using high-dose glucocorticosteroid (GCS) (methylprednisolone 30 mg/kg/day, intravenously) as a proactive anti-inflammatory

therapy [4]. It has been shown that early use of high-dose methylprednisolone at the onset of respiratory insufficiency can slow the progression of the process in patients with COVID-19. At the same time, studies have found no pronounced positive effect of GCS use in the management of patients with viral lung lesions [5]. It was noted that GCS use could cause increased lethality and prolong of the disease and causative prolongation of the viral load period. It should be noted that the vast majority of studies are based on the results of patients with influenza, SARS-CoV1 and MERS-CoV [5].

GCS is one of the most popular anti-inflammatory agents, with a long history of use; the effectiveness of GCS therapy in patients with COVID-19 pneumonia and cytokine storm is of scientific interest and practical significance. This study aimed to evaluate the efficacy of pulse dose steroid therapy with methylprednisolone on inflammatory markers and mortality in ICU patients with COVID-19 pneumonia.

Material and methods

We performed a single center, retrospective study between 12 November 2020 and 31 December 2020. The study included 197 patients hospitalized at the Republic of Turkey Health Sciences University, Bursa Yüksek Ihtisas Training and Research Hospital COVID-19 ICU with a proven diagnosis of coronavirus pneumonia related respiratory failure and cytokine storm. The diagnosis in all cases was confirmed by detection of SARS-CoV-2 RNA by polymerase chain reaction (PCR).

Treatment protocol

Patients whose oxygen saturation was below 90 or whose respiratory rate was above 35/min with a reservoir oxygen mask under a flow of 15 liters/min were diagnosed as COVİD-19 pneumonia related respiratory failure and admitted to the intensive care unit as stated in local guidelines [4]. Initially, standard therapy was prescribed with hydroxychloroquine and favipiravir. In addition, all patients received anticoagulant therapy with LMWH and antithrombotic therapy with ASA from the first day of hospitalization, as stated in local guidelines. If necessary, antibiotic therapy was added to the therapy.

Cytokine storm defined at least two hyperferritinemia, hyperfibrinogenemia, high levels of D-dimer, and CRP with respiratory failure. The treatment decision with one dosage or another was exclusively at the discretion of the treating medical team. The attending physicians decided to treat patients in cytokine storm with high doses of GCS: methylprednisolone 250-500-1000 mg intravenously for 3-5 days with the transition to methylprednisolone 1 mg/kg/day twice a day for 5-7 days or standard dose of GCS with methylprednisolone 1 mg/kg/day for 7-10 days [4]. It was decided to use a pulse or standard dose drugs based on inflammatory markers of cytokine storm rather than oxygenation status (Table 1).

Table 1 COVID-19 Glucocorticosteroid treatment protocol in macrophage activation syndrome or severe respiratory insufficiency recommended by MOH of Republic of Turkey (9 October 2020)

	Standard dose	Pulse Dose
Methylprednisolone*	0,5-1 mg/kg/day (10 days)	>250 mg/day (3-5 days) than 1 mg/kg/day (7 days)
Dexamethasone	6 mg/day (10 days)	
*only methylprednisolone used patients included the study		

We recorded demographic data, acute physiologic and chronic health evaluation APACHE2 score, comorbidities, length of stay in ICU, need for invasive ventilation and intubation, death in ICU and dose of GCS were given. Other specific anti-inflammatory therapies like monoclonal antibodies, plasmapheresis or IVIG were also noted. The duration of follow-up in both groups was until deceased or discharged from ICU.

Neutrophil and lymphocyte count, glomerular filtration rate, creatinine kinase, lactate dehydrogenase, ferritin, international normalized ratio (INR), D-dimer, prothrombin time (PT) and partial thromboplastin time (aPTT), C-reactive protein (CRP) levels were recorded before the initiation of GCS therapy (1st day), 4th and 7th days of GCS therapy. Due to the limited availability of interleukin 1 and 6 diagnostic kits in the hospital, these parameters are not routinely studied. Therefore, they were not included in the study protocol.

Ethics

The study was initiated after obtaining the ethics committee approval no. 2011-KAEK-25 2021/03-28 from TC SBU Bursa Yüksek Ihtisas TRH. The need for informed consent from individual patients from waived due to its retrospective design.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS) for Windows 22.0 (IBM Corp., Armonk, NY) package program.

The normality of the data was tested using the Shappiro-Wilk test. Quantitative data description is presented as the median and interquartile range (median and 25%; 75%). Qualitative data are presented as absolute and relative values. The significance of differences between groups in qualitative characteristics was assessed using the $\chi 2$ criterion and two-sided Fisher exact test.

A comparison of quantitative characteristics between the groups was performed using the Mann-Whitney test. The critical level of significance for statistical testing hypotheses was taken to be <0.05.

Results

Characteristics of the cohort

We recruited 197 adult patients between the specified dates. The mean age was 64.19±13.28, ranging from 25 to 92 years. 114 were men (57.86%) and 83 were women (42.13%).

Hypertension and diabetes mellitus were present in a (n:98) 49.74% and (n:50) 25.83% of the patients respectively. Other comorbid conditions were infrequent (less than 10%) and did not show any statistically significant differences between groups. The initial characteristics of the examined patients are presented in Table 2.

Study endpoint

We aimed to investigate whether pulse dose steroid was effective in COVID-19 ICU patients or not. In our cohort, pulse dose steroids did not decrease the mortality in ICU; also, standard dose steroids had a better survival ratio in ICU (Table 3). Endotracheal intubation need in whom receiving HFNO and NIV in ICU in pulse dose steroid group was statistically higher ($p<0.01$).

Time course analysis of laboratory markers

We carried out a time course analysis between 1st and 7th day of COVID-19 related cytokine storm pro-inflammatory markers: Ferritin, Lactate dehydrogenase (LDH), D-dimer and

Table 2 Demographic data

			Pulse dose n:144	Standard dose n:53	p
Age ($\bar{X}$±Ss)			63.58±13.02	65,85±14,82	0.30
Sex	Male	n%	88a 61.1%	26a 49.1%	0.12
	Female	n%	56a 38.9%	27a 50.9%	
Comorbidities	Yes	n%	103a 71.5%	44a 83.0%	0.1
	No	n%	41a 28.5%	9a 17.0%	
IMV need in ICU	Yes	n%	78a 54.2%	12b 22.6%	0.01
	No	n%	66a 45.8%	41b 77.4%	
O2 support	NIV	n%	25a 17.4%	2b 3.8%	X2: 8.81, p:0.01
	IMV	n%	34a 23.6%	21b 39.6%	
	HFNO	n%	85a 59.0%	30a 56.6%	
ICU LOS			12.62±6,92	10.08±6,40	0.02
APACHE 2 ($\bar{X}$±Ss)			22.99±5,70	23,53±5,81	0.56

O2: Oxygen; IMV: Invasive Mechanical Ventilation; NIV: Non-invasive Mechanical Ventilation; HFNO: High Flow Nasal Oxygenation Therapy; ICU: Intensive Care Unit; LOS: Length of Stay; APACHE: Acute Physiologic and Chronic Health Evaluation

Table 3 Mortality in groups

			Deceased	**Discharged**	**Total**	***p***
Pulse dose		n %	109a 76,8%	35a 63,6%	144 73,1%	0,06
Standard dose		n %	33a 23,2%	20a 36,4%	53 26,9%	
Pulse steroid dosage	250 mg/d	n %	75a 68,8%	30a 85,7%	105 72,9%	0,1
	500 mg/d	n %	7a 6,4%	0a 0,0%	7 4,9%	
	1000 mg/d	n %	27a 24,8%	5a 14,3%	32 22,2%	

C-reactive protein (CRP), fibrinogen (Fib). Due to the utility in clinical decision making, we also highlight overall time differences in platelets, total neutrophils, total lymphocytes. When we evaluated pro-inflammatory markers, a statistically significant decrease was found in the some parameters in both groups over time (Table 4).

Discussion

We did not find any statistical difference between pulse dose and standard dose steroid groups in survival in COVID-19 patients with severe pneumonia with cytokine storm in the ICU. In addition, we found that patients who received standard doses were discharged from the ICU at a higher rate and stay shorter in ICU. In addition, we found that inflammatory markers decreased compared to baseline values in both groups.

COVID-19 goes through different stages, each of which requires different therapeutic approaches. Each stage requires a different treatment approach. At the stage of advanced viral pneumonia with alveolar damage, the problem is aggravated by the progression of systemic inflammation and the involvement of the pulmonary parenchyma and bronchioles, small vessels, and increased thrombogenesis. In these cases, immune system hyperreactivity is accompanied by excessive cytokine activation, further activation of macrophages and epithelial cells, and permanent cytokines and chemokines called "cytokine storm" [6,7].

Table 4 Pro-inflammatory markers in COVID-19

	Pulse Dose	Standard Dose	*p*
Fibrinogen 1st day	2,42	2,5	0,05
Fibrinogen 4th day	1,79	2,1	0,68
Fibrinogen 7th day	1,79	1,4	0,02
	***p:0,01*	***p:0,01*	
D-Dimer 1st day	2,01	2,14	0,82
D-Dimer 4th day	2,05	2,08	0,19
D-Dimer 7th day	1,94	1,78	0,02
	***p:0,61*	***p:0,12*	
Ferritin 1st day	2,12	2,07	0,06
Ferritin 4th day	1,94	2,15	0,16
Ferritin 7th day	1,94	1,78	0,01
	***p:0,19*	***p:0,13*	
LDH 1st day	2,01	2,21	0,27
LDH 4th day	2,15	2,17	0,09
LDH 7th day	1,84	1,62	0,01
	***p:0,03*	***p:0,01*	
CRP 1st day	2,48	2,6	0,44
CRP 4th day	1,67	1,91	0,44
CRP 7th day	1,85	1,49	0,01
	***p:0.01*	***p:0.01*	
Neutrophil 1st day	1,77	1,94	0,67
Neutrophil 4th day	2,12	2,23	0,49
Neutrophil 7th day	2,1	1,83	0,94
	***p:0.01*	***p:0.1*	
Lymphocyte 1st day	2,42	2,28	0,51
Lymphocyte 4th day	1,81	1,99	0,01
Lymphocyte 7th day	1,77	1,73	0,69
	***p:0.01*	***p:0.01*	

LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein

**Mann Whitney-U test ** Friedman test*

This study is devoted to treating such patients in ICU with COVID-19 pneumonia and cytokine storm. Recommendations suggest using "pro-active anti-inflammatory therapy" in such cases to relieve "cytokine storm" and overcome critical inflammation [8]. WHO has not recommended the use of the most popular anti-inflammatory drugs (GCS) in COVID-19. The guidelines of Turkish MoH specify the possible use of GCS at low doses up to 1 mg/kg/day until November 2020. The published guideline on 11 November stated that pulse/high dose could be used in patients with cytokine storm [4].

Systemic GCS's have always been controversial in treating viral pneumonia. A meta-analysis demonstrated that GCS treatment was associated with longer length of stay, higher probability of bacterial infection, and mortality among patients with coronavirus pneumonia [9]. In addition, whether systemic GCSs delay viral clearance is another topic of priority. The first randomized controlled trial about GCSs and viral clearance observed that patients with early use of hydrocortisone harbored higher plasma SARS-CoV viral load and a long time of viral shedding than those without hydrocortisone [10]. Sijia Li et al. [11] showed that high dose of metyhlprednisolone may delay viral shedding in COVID-19 patients.

However, pulse therapy with high doses of GCS in early therapy of SARS showed a delay in disease progression, better resolution of lung changes with a low risk of side effects [12,13]. Limitations of GCS use are their ability to increase prothrombotic factors, especially in immune inflammation, which occurs in COVID-19 with "cytokine storm" [1,14]. Studies link the risk of VTE during therapy with steroid hormones with the doses of preparations, with the maximum risk increase noted at doses from 1000 to 2000 mg/day [15].

Our study aimed to study the efficacy of GCS pulse therapy (250-500-1000 mg of methylprednisolone for 3-5 days intravenously with 1 mg/kg/day methylprednisolone for 5-7 days) in the treatment of patients in ICU with severe COVID-19 pneumonia compared with the group of patients receiving standard dose GCS (1 mg/kg/day for 7-10 days) therapy. Analysis of the examined patients in both groups showed signs of systemic inflammation with an extreme increase of CRP, ferritin, fibrinogen and D-dimer. Patients in the control group had the same severe course of the disease according to the majority of studied parameters.

Our study failed to confirm the possible effectiveness of PDS therapy in treating COVID-19 pneumonia with cytokine storm in ICU patients. Statistically insignificantly but more significantly in the PDS group, survival in ICU (primary endpoint of the study) decreased. Also, in the study group, there was a significant increase in invasive mechanical ventilation need. Even though reduction of CRP levels on 4th day, which characterized the rapid anti-inflammatory effect of high doses of GCS, increased on 7th day. There was a progression of hypoxia and a significant increase in the need for IMV. Trahmerteg [16] offer that there was a spectrum of reactivity with high prevalence in the extensive panel of autoantibodies in patients with respiratory failure and patients with COVID-19-induced respiratory failure have similar autoantibody profiles as contemporaneous. Therefore, steroid administration alone may not have prevented the progression to respiratory failure.

The second objective of the study was to assess the inflammatory markers of COVİD 19. D-dimer dynamics appeared to be the most problematic. Previous studies have demonstrated that a D-dimer increase above 2.0 µg/ml increases VTE risk in patients with COVID-19 by 51 times [17]. Zhou et al. [18] demonstrated that even D-dimer increase above 1.0 µg/mL significantly increased the risk of thrombosis by 18 times. In our findings the D-dimer decreased in standard dose group rather then pulse dose group on 7th day (p:0.02). It is known that GCS can cause leukocytosis and neutrophilia [19]. In our study, the neutrophil count increased from 1st day to 7th day (p:0.01) during pulse GCS treatment, while there were no changes in the SDS group. Lymphopenia persists in both groups. Thus, despite the rapid decrease of acute inflammation, the use of GCS provokes the growth of neutrophilia and lymphopenia (increases in N/L index), which leads to a statistically significant increase of thrombosis and TE risk, which is indicated by significant growth of D-dimer. Although we did not analyze the N/L index and correlation between changes in N/L index and D-dimer in our study, it has been stated that it is an inflammation marker and a predictor of VTE and TE [20]. The N/L index can predict both COVID-19 severity and unfavorable prognosis [21,22]. At the maximum N/L index increase (4.85-88.09), the risk of death in patients with coronavirus pneumonia increases 15-fold [23]. The N/L index value reflects activation of chronic inflammation and autoimmune endothelial inflammation and may cause the unfavorable course of COVID-19 [24].

Our results showed D-dimer significantly high in the pulse dose group (p:0.02). Our patients in this study received the same dose of anticoagulant (enoxaparin 0.01 IU/kg BID) and antithrombotic (ASA 100 mg/day) therapy. Because this is very difficult to determine, we do not know precisely how many thromboembolic events were seen in patients as the cause of death. Therefore, when choosing pulse steroid therapy as an anti-inflammatory response to "cytokine storm" in patients with COVID-19 pneumonia, D-dimer levels should be considered, strengthening anticoagulant therapy should be necessarily considered.

Limitation

Our study was a retrospective chart analysis from a single center study with a limited sample size. The most important limitation was that the doses given are in the choice of the clinician. Also, we did not study viral elimination, which is the primary concern of using steroids.

Conclusion

If the course COVID-19 pneumonia is persistent and inflammatory markers increase, it may not successfully be cured without anti-inflammatory drugs. Our results showed that PDS therapy could interrupt the cytokine storm. However, the results of our study with COVID-19 did not confirm the improvement of prognosis in ICU. This led to the recommendation of using anti-cytokine drugs rather than GCS, which can also slow down eliminating the virus during COVID-19 treatment.

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Can immature granulocytes be used as a predictive new marker in the diagnosis of acute cholecystitis?

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Abstract

Aim: Acute cholecystitis (AC) is one of the most common acute surgical diseases in the emergency department (ED). The aim of this study was to investigate the efficacy of inflammatory parameters as immature granulocyte count (IGC) and immature granulocyte percentage (IG%) in the diagnosis of AC.

Material and methods: This retrospective and observational study consisted of patients, diagnosed with AC, who were admitted to a tertiary ED with abdominal pain between March 2019 and April 2021. The effectiveness of IGC and IG% in the diagnosis of AC was examined by comparing the results with the control group (CG).

Results: A total of 493 patients were included in the study. 270 patients were in the AC group, 223 patients were in the CG. IG% and IGC were found to be significantly higher in the AC group than in the CG (0.5 (0.32) vs. 0.4 (0.2); 0.06 (0.08) vs. 0.03 (0.03); p<0.001, p<0.001 respectively). It has been shown that IGC, at a cut-off value of 0.03, predicts the diagnosis of AC with 72.1% sensitivity and 55.5% specificity. On the other hand, IG%, at a cut-off value of 0.45, predicts the diagnosis of AC with 53.2% sensitivity and 72.7% specificity (AUC [0.717 (0.672-0.762); 0.692 (0.645-0.738)], respectively p<0.001, p<0.001).

Conclusions: In conclusion, IGC and IG% can be used as a useful inflammatory parameter in the diagnosis of AC in patients admitted to the emergency department.

Key words: immature granulocyte, acute cholecystitis, emergency department

Introduction

Abdominal pain is one of the most common complaints in the emergency department (ED). Many abdominal pain generally to have a benign etiology [1]. However a sign of local inflammation (Murphy sign or right upper quadrant pain, tenderness) should reveal the suspicion of acute cholecystitis.

Acute cholecystitis (AC) is a common complication of gall bladder stones and is one of the most common acute surgical diseases [2]. Although the general prevalence of gallstones varies between countries, it is estimated to be in 10%-15% of the general population. As a complication related to gallstones, calculosis AC occurs with an annual incidence of 1%-3% [3]. Cystic duct obstruction generally develops in these patients, due to gall bladder stones, which results with edema and inflammation in the gallbladder. The disease is an emergency surgical situation and mortality and morbidity increase in delayed surgical cases due to complications accompanied by gangrenous cholecystitis and gallbladder perforation [4]. Therefore, a detailed physical examination and history, laboratory tests, and extensive radiological imaging is needed in patients with suspected AC. One of the radiological imaging methods, such as USG/CT or Magnetic resonance imaging (MRI), is needed for definitive diagnosis in the case of AC clinical suspicion [1]. Clinical classification that includes radiological imaging findings of inflammation together with clinical markers is often useful, for the diagnosis of AC as suggested by The Tokyo Guidelines (TG 18) [5]. However, in cases where radiological imaging is not possible; laboratory tests for new inflammatory markers such as bedside Neutrophil-to-lymphocyte ratio (NLR) may be useful [6]. Immature granulocyte, one of these new inflammatory markers, is an indicator of increased myeloid cell production and it has been shown to increase in inflammatory conditions [7, 8]. In recent studies in the literature, it has been shown that immature granulocyte count (IGC) and immature granulocyte percentage (IG%)

are useful as inflammatory markers in many diseases such as acute pancreatitis accompanied by inflammation, acute appendicitis, acute gastrointestinal hemorrhage and intracerebral hemorrhage [9-12]. There is no study yet showing the predictivity of IGC and IG% in the diagnosis of AC. Therefore, the purpose of the study was to investigate the effectiveness of IGC and IG% as a diagnostic marker in AC patients.

Material and methods

This retrospective and observational study consisted of patients, diagnosed with acute cholecystitis (AC), who were admitted to a tertiary emergency department (ED) with abdominal pain between March 2019 and April 2021. The Control group (CG) had patients who were admitted to the ED with non-specific abdominal pain. CG was randomly determined and was similar in age and gender to AC patients. Approval with the date and decision number as 24/06/2021-9/16 was obtained from the local ethics committee.

Study design and participants

All patients who applied to the emergency department with abdominal pain during the study were retrospectively screened. Radiological imaging was performed using abdominal ultrasonography (USG) or abdominal computed tomography (CT) to patients with clinically suspected AC by an emergency specialist in the emergency department. Laboratory parameters were studied at the time of admission to the emergency department. The diagnosis of AC was made after consulting a general surgeon by following the criteria below: A. A sign of local inflammation (Murphy sign or right upper quadrant pain, tenderness) B. Signs of systemic inflammation (fever, elevated CRP, elevated leukocyte count) C. Imaging findings (characteristic USG or CT finding for AC). The diagnosis of AC was confirmed by the presence of at least one of the B or C criteria along with an A criterion [5]. All patients <18 years of age, pregnant patients, patients with hematological malignancies that may change hematological parameters, patients using granulocyte colony stimulating factor, immunosuppressive agents or steroids, patients with post-traumatic abdominal pain and patients with incomplete data were excluded from the study. The CG consisted of patients without a diagnosis of AC. Patients were categorized into two groups as AC and CG.

Data collection and measurements of variable

The records of the patients were scanned through the electronic data-based hospital information system. Complete blood count (CBC) analysis was performed with the Sysmex XN-1000 (Sysmex Corp., Kobe, Japan) device at the time of patients' admission to the emergency department. WBC, neutrophil, platelet, lymphocyte, IGC, IG%, CRP, and biochemistry [aspartate aminotransferase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), amylase, lipase, total bilirubin, direct bilirubin, glucose, blood urea nitrogen (BUN)] platelet distribution width (PDW) and Red cell distribution width (RDW) were recorded. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated from CBC results.

Outcomes

As a primary outcome, the predictivity of IGC and IG% in the diagnosis of AC was evaluated by comparing it with the control group.

Statistical analysis

All variables were evaluated using descriptive statistics. Standard deviation and mean values were calculated for continuous variables, and median and interquartile ranges were given. Each independent variable was compared using the chi-square test and the independent t test were used for continuous variables. Descriptive statistical analysis of all variables was made using the SPSS 20.0 program. Optimal cut-off value of IGC and IG % parameters as a diagnostic biomarker in the diagnosis of acute cholecystitis was analyzed by Receiver operating characteristic (ROC) analysis.

Results

A total of 493 patients were included in the study. 270 patients were in the AC group, 223 patients were in the CG. The mean age of the patients was 58.49±16.48 years in the AC group and 39.94±14.25 years in the CG. The mean age of the patients was significantly higher in the AC group ($p<0.001$). Among the male patients, 133 (49.3%) were in the AC group and 74 (33.2%) were in the CG. There was a significant difference between the groups in terms of gender ($p<0.001$). The mean WBC count was found to be significantly higher in the AC group than in the CG (12.84±5.42 vs. 9.41±3.05; $p<0.001$). The mean CRP level of the patients was found to be significantly higher in the AC group than in the CG (47 (139) vs. 4 (10); $p <0.001$).

Figure 1 - Comparision of immature granulocyte count (IGC) levels between healthy control and acute cholecystitis groups

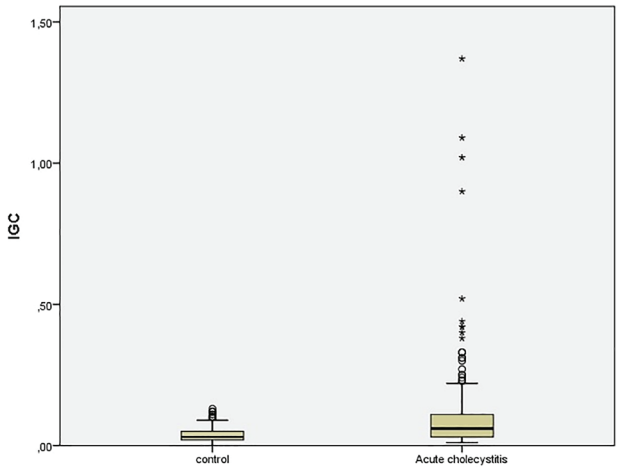


Figure 2 - Comparision of immature granulocyte percentage (IG%) levels between healthy control and acute cholecystitis groups

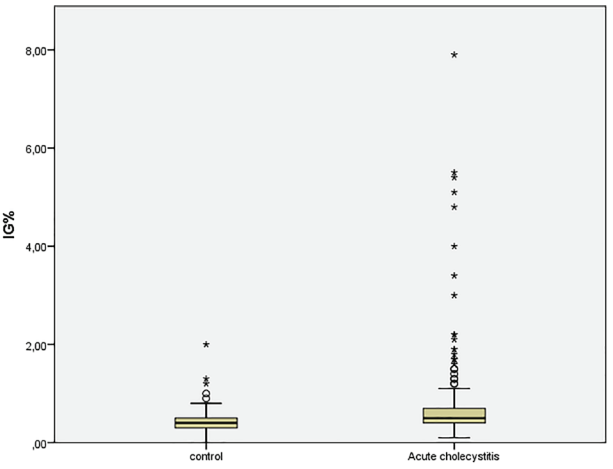


Table 1 Baseline of acute cholecystitis (AC) patient and healthy control groups

	Patient (n=270)	Control (n=223)	*P* value
Age (years)(mean±SD)	58.49±16.48	39.94±14.25	<0.001
Male, n (%)	133 (49.3)	74 (33.2)	<0.001
Laboratory tests(mean±SD)			
WBC count (×103/mm3)	12.84±5.42	9.41±3.05	<0.001
Hemoglobin (mg/dL)	13.02±2.01	13.22±2.06	0.221
PDW(fL; mean ± SD)	12.51±2.25	11.41±2.80	<0.001
RDW(fL; mean ± SD)	14.07±1.93	13.43±2.03	<0.001
PLT (×103/mm3)	261.96±86.57	274.89±77.57	0.59
Neutrophil, (×103/mm3)	9.97±5.26	6.20±3.04	<0.001
Lymphocyte, (×103/mm3)	1.73±0.98	2.31±1.01	<0.001
NLR	8.81±1.11	3.83±1.29	<0.001
PLR	205.97±163.05	150.64±121.97	<0.001
IG% (IQR)	0.5 (0.32)	0.4 (0.2)	<0.001
IG count (×103/mm3 (IQR)	0.06 (0.08)	0.03 (0.03)	<0.001
Glucose (mg/dl)	138.62±65.05	105.45±35.14	<0.001
BUN(mg/dL)	18.06±12.00	13.41±5.24	<0.001
Creatinine (mg/dl) (IQR)	1.09±0.89	0.88±0.26	0.31
CRP (mg/dL) (IQR)	47 (139)	4 (10)	<0.001
ALT(IU/L) (IQR)	31 (75)	18 (13)	<0.001
AST(IU/L) (IQR)	34 (84)	23 (9)	<0.001
GGT(IU/L) (IQR)	51 (173)	18 (13)	<0.001
Total bilirubin (mg/dl) (IQR)	0.94 (1.36)	0.45 (0.38)	<0.001
Direct bilirubin (mg/dl) (IQR)	0.20 (0.68)	0.08 (0.05)	<0.001
Lipase (IU/L) (IQR)	21 (27)	20 (18)	0.186

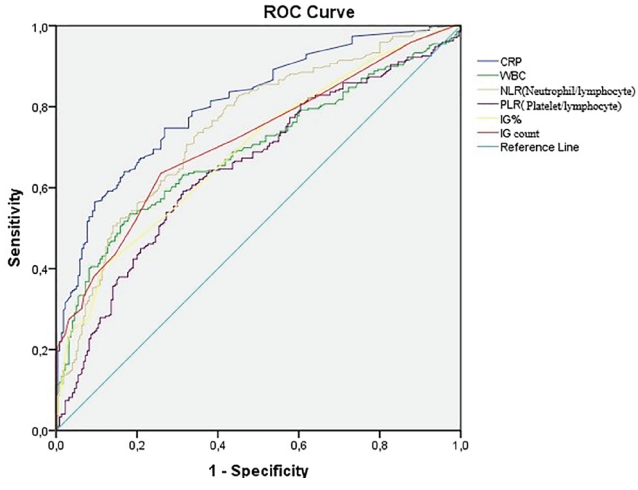
WBC: White blood cell; **CRP:** C-reactive protein; **IG:** Immature granulocytes **BUN:** Blood urea nitrogen
PLT: Platelet count **NLR:** Neutrophil-to-lymphocyte ratio; **PLR:** Platelet-to-lymphocyte ratio;
PDW: Platelet distribution width; **RDW:** Red cell distribution width
ALT: Alanine transaminase **AST:**Aspartate aminotransferase **GGT:** Gamma Glutamyltransferase

Table 2 Diagnostic predictors of acute cholecystitis

	AUC	95% CI	CUT-OFF	SEN (%)	SPE (%)	p
WBC	0.690	0.644-0.737	10.71	57.2	73.2	<0.001
CRP	0.808	0.770-0.845	10.25	71.7	74.1	<0.001
NLR	0.747	0.704-0.791	3.49	66.9	69.2	<0.001
PLR	0.650	0.602-0.699	160.59	53.9	72.7	<0.001
IG%	0.692	0.645-0.738	0.45	53.2	72.7	<0.001
IGC	0.717	0.672-0.762	0.03	72.1	55.5	<0.001

AUC: Area under the curve; **CI:** Confidence interval; **SEN:** Sensitivity; **SPE:** Specificity; **WBC:** White blood cell; **CRP:** C-reactive protein; **IGC:** Immature granulocytes count **IG:** Immature granulocytes **NLR:** Neutrophil-to-lymphocyte ratio; **PLR:** Platelet-to-lymphocyte ratio

Figure 3 - Receiver operating characteristic (ROC) curve of immature granulocyte and other inflammation parameters for predicting acute cholecystitis.



Besides, the mean IG% and IGC was found to be significantly higher in the AC group when compared with CG (0.5 (0.32) vs. 0.4 (0.2); 0.06 (0.08) vs. 0.03 (0.03); p <0.001, p <0.001 respectively) (Figure 1, Figure 2). The mean value of NLR and PLR were found to be significantly higher in the AC group than in the CG (8.81±1.11vs. 3.83±1.29; 205.97±163.05 vs. 150.64±121.97, respectively p<0.001). Table 1 shows the relationship between the baseline characteristics and other laboratory parameters of AC patients with the CG. ROC analysis was performed to show the predictive efficacy of IGC, IG%, WBC, CRP, NLR and PLR in the diagnosis of AC. Area under the curve (AUC) was calculated for each parameter and was found to be statistically significant in the diagnosis of AC (Figure 3). CRP had the highest AUC (0.808; p<0.001). AUC value was found to be statistically significant for NLR, IGC, IG%, WBC and PLR following CRP (AUC=0.747, 0.717, 0.692, 0.690 and 0.650). It has been shown that IGC, at a cut-off value of 0.03, predicts the diagnosis of AC with 72.1% sensitivity and 55.5%

specificity. On the other hand, IG%, at a cut-off value of 0.45, predicts the diagnosis of AC with 53.2 % sensitivity and 72.7% specificity (AUC: 0.717 (0.672-0.762); 0.692 (0.645-0.738), respectively p<0.001, p<0.001) (Table 2).

Discussion

The results of our study showed that IGC and IG% are useful in the diagnosis of AC compared to other inflammation parameters. The AC prediction ability of IGC and IG% was revealed with similar sensitivity and lower specificity compared to CRP, which has the highest sensitivity and specificity. Therefore, this study was found to be important in guiding the clinician in terms of accepting IGC and IG% as a new inflammatory parameter in the diagnosis of AC.

Recently, IG can be measured as an infection marker with an easy, cheap and fast method with new generation automatic hemogram devices [13]. IG cells are not physiologically found in the circulation. However, studies have shown that immature granulocyte is a useful marker in diseases accompanied by inflammation [14, 15] Since there is no feature strong enough to diagnose or exclude AC; evaluation of clinical or laboratory results alone is not recommended by current guidelines. Combination with detailed history, physical examination and laboratory tests and imaging is recommended [3]. USG imaging has been the first preferred diagnostic imaging method in many guidelines [16]. In fact, its diagnostic efficiency has been demonstrated with a high sonographic AC score in a prospective bedside USG validation study [17]. However, USG imaging is operator-dependent, and it can be difficult to diagnose AC in the emergency department because it requires patient compliance. Other laboratory tests are needed along with the clinic. Therefore, researchers have focused on new inflammatory parameters in the diagnosis of AC since there is no specific laboratory parameter. Studies have shown that NLR and PLR are as useful as CRP in the diagnosis of AC. In a study of Bedel C. [6], it was shown that NLR, with the highest sensitivity 94.4% and AUC (0.846; p<0.001), followed by PLR with 77.9% sensitivity and AUC (0.768; p<0.001) are diagnostically effective. Similar to Bedel's study, NLR and PLR were found to be statistically significant in the diagnosis of AC in present study. In another study on the role of NLR in the differentiation of AC and complicated AC; NLR was found as a diagnostic parameter with 80.9% positive predictive value and AUC (0.736; p<0.001) [18]. However, when we searched the literature, there is no study on IG in the diagnosis of AC yet. In many studies, the prognostic and diagnostic relationship of IG in diseases accompanied by inflammatory processes has been examined. Recent studies have also demonstrated the prognostic value of IG. In a study of Barut et al. [19], in which the prognostic value of IG was evaluated in gall bladder cancer, IGC was found as significant with 83.6% sensitivity and 84.2% specificity at 0.08 cut-off value and AUC: 0.910 [95% CI 0.858-0.962]. In a study of Unal et al. [11], it was determined that IG could distinguish complicated appendicitis from simple appendicitis at a cut-off value of 0.1. In another study of Güngör et al. [13], IG has been shown to be effective in differentiating acute complicated appendicitis from simple appendicitis, with a sensitivity of 85.4% at a cut-off value of 0.35% and AUC: 0.82 [95% confidence interval (CI) 0.77–0.87]. In present study, IGC and IG% was found to be effective in the diagnosis of AC at cut-off value of 0.03 and 0.45, respectively.

The present study has some limitations. First, this study was designed in a retrospective nature at a single center with a small number of patients. The second important limitation is that IG was measured only during admission. Serial measurements were not made at certain time intervals starting from the onset of symptoms until the diagnosis. Our recommendation to the researchers is to carry out further studies in a prospective manner with wide-ranging population at multi centers.

Conclusion

In conclusion, IGC and IG% can be used as a useful inflammatory parameter in the diagnosis of AC in patients admitted to the emergency department.

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Seroprevalence of SARS COV-2 anti-nucleocapsid antibodies in Turkish healthcare workers before vaccination schedule: January 2021

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Abstract

Objective: We aimed to assess the seroprevalence of SARS-CoV-2 infection and associated factors among Turkish HCWs, before the Covid-19 vaccination program in January 2021.

Material and methods: We performed antibody assessment against SARS-CoV-2 in blood samples from participants using the Elecsys® Anti-SARS-CoV-2 electrochemiluminescence immunoassay. Samples with a cut-off index (COI; signal sample/cut-off) <1.0 were considered negative, samples with ≥1.0 were deemed positive.

Results: 714 HCWs, 487 women (68.2%), were included in our study. The mean age of the participants was 35.9 ± 8.4 (min:18, max: 62). 370 (51.8%) HCWs's the antibody level was negative, and 344 (48.2%) was positive. While 47.1% (n=122) of the HCWs with positive RT-PCR were antibody positive, 48.8% (n=222) were negative. There was no statistically significant difference in mean age and age groups (p values 0.338 and 0.414, respectively). Also, there was no statistically significant difference in antibody levels by gender (p=0.236). There was no significant difference between antibody positivity according to the presence of comorbidity, and the risk area studied (p=0.556, p=0.335, respectively). There was a statistically significant difference between lung involvement and antibody positivity during Covid-19 infection (p= <0.001).

Conclusion: In our study, the seroprevalence of SARS-CoV-2 antibodies in HCWs was higher than the average population and approximately fifty percent. Multicenter studies with more HCWs would be helpful to determine overall seroprevalence rates.

Key words: COVID-19, SARS-CoV-2 antibody, healthcare worker

Introduction

The ongoing Covid-19 pandemic; According to the data of the World Health Organization, as of October 2021, it caused more than 240 million confirmed cases and over 4.8 million deaths [1]. This period reported 65 thousand deaths and 7 million patients in Turkey [2].

The diagnosis of SARS-CoV-2 infection is based on the presence of viral nucleic acid or antigen by nucleic acid amplification tests such as reverse transcription-polymerase chain reaction (RT-PCR) in the respiratory tract samples, mainly in the nasopharynx [3,4]. Especially in asymptomatic or subclinical infections, it is estimated that many patients could not be diagnosed with Covid-19 due to the lack of PCR testing. The best method in diagnosing cumulative incidence of infection in a population is the detection of anti-nucleocapsid antibodies [4]. Healthcare workers (HCWs) are particularly vulnerable as they care for patients with unknown COVID-19 status. Also, HCWs perform high-risk procedures for covid-19 transmissions, such as endotracheal intubation and cardiopulmonary resuscitation.

We aimed to evaluate the SARS-CoV-2 anti-nucleocapsid antibody level and affecting factors in Turkish HCWs before the Covid-19 vaccination program.

Material and methods

Study design and patients

We conducted this study in Kayseri City Training and Research Hospital on January 18, 2021. The study included all volunteered HCWs. Participants answered a questionnaire that included medical history, occupation, risk groups according to the study area, and their symptoms during the illness if they had COVID-19 recently. We defined risk groups as low, middle, and high according to the study area. The low-risk group included medical secretary, cleaning and support staff working standard wards, working office, store, or kitchen; the middle-risk group lab/radiology technicians, cleaning and support staff working COVID-19 ward. And doctors and nurses were in the high-risk group. All participants signed an informed consent form. The Bio-speedy SARS-CoV-2 (2019-nCoV) RT-qPCR detection kit (Bioeksen, Istanbul, Turkey) was used in the SARS-CoV-2 PCR test on nasopharyngeal swabs to determine the presence of SARS-CoV-2 infection.

Antibody assessment

Elecsys Anti-SARS-CoV-2 electrochemiluminescence immunoassay test used. This assay is intended for use on Cobas e analyzers (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) for the in vitro qualitative detection of antibodies (both IgA and IgG) to SARS-CoV-2 in human serum and plasma. The Elecsys Anti-SARS-CoV-2 test uses the double antigen sandwich test principle and a recombinant protein representing the nucleocapsid antigen to detect antibodies to SARS-CoV-2. Anti-SARS-CoV-2 antibody per manufacturer's instructions: samples with a cut-off index (COI; signal sample/cut-off) <1.0 were considered negative, samples with ≥1.0 were deemed positive. A measured antibody level magnitude above the cut-off value is not considered an indicator of the sample's total amount of antibody present.

Sample size estimation

Based on the assumption that approximately 40% of healthcare professionals will have antibody positivity, we calculated the required sample size as 369 with a 95% confidence interval and 5% margin of error using the Statcalc calculator program in Epi Info (version 7.2.5.0).

Statistical analysis

Categorical data were summarized as frequency and percentage, continuous data with normal distribution as mean ± standard deviation, and data, not with normal distribution as median, 25%-75% interquartile range (IQR). We used the Shapiro Wilk test for normality controls of continuous measurements. We used independent sample t-tests to compare the regular and Mann-Whitney-U tests for the non-regular distributed two groups. And to compare categorical variables, the Chi-square test was used. The statistical significance level was 0.05.

Ethics approval

The Ethics Committee of the Kayseri City Hospital approved this study (Approval no: 59-11022022).

Results

A total of 714 HCWs, 487 women (68.2%), were included in our study. The mean age of the participants was 35.9±8.4 (min: 18, max: 62). Of the participants, 425 (59.5%) were nurses, 106 (14.8%) were medical secretaries, and 106 (14.8%) were physicians. When the participants were categorized in terms of SARS-CoV-2 transmission risk, 14.8% (n=106) low, 10.8% (n=77) moderate, 74.4% (n=531) high was in the risk group. At least one comorbid disease in 135 (18.9%) of the participants. The most common comorbid diseases were hypertension (3.5%), autoimmune diseases (3.5%), and diabetes (2.9%) (Table 1).

Two hundred and fifty-nine (36.2%) participants had previously been positive for SARS-CoV-2 RT-PCR, and lung involvement occurred in 11.2% (n=29).

Table 1 Demographic and Clinical Characteristics of HCWs

Age, mean (± SD), years	35.9 ± (8.4)	
Gender	n	**(%)**
Female	487	(68.2)
Male	227	(31.8)
Age Groups		
18-40	505	(70.7)
41-50	177	(24.8)
>51	32	(4.5)
Job groups		
Doctor	106	(14.8)
Nurse	425	(59.5)
Medical secretary	106	(14.8)
Lab/radiology technician	66	(9.2)
Cleaning and support staff	11	(1.5)
Risk groups according to the study area		
Low	106	(14.8)
Middl e	77	(10.8)
High	531	(74.4)
Comorbit diseases	**135**	**(18.9)**
Hypertension	25	(3.5)
Diabetes mellitus	21	(2.9)
Chronic obstructive pulmonary disease	19	(2.7)
Coronary artery disease	6	(0.8)
Autoimmune diseases	25	(3.5)
Malignancy	3	(0.4)
Hypothyroidism	15	(2.1)
Other	12	(1.7)
Antibody level		
COI <1.0	370	(51.8)
COI ≥1.0	344	(48.2)
RT-PCR history		
Negative	455	(63.8)
Positive	259	(36.2)
	Median	**IQRs 25-75% (min-max)**
Days from PCR positivity to the day of antibody testing	82	43-132 (2-314)
Symptoms of RT-PCR positive patients (n= 259)	n	%
Fever	34	(16.1)
Cough	56	(26.5)
Throat ache	32	(15.1)
Shortness of breath	21	(9.9)
Weakness	40	(18.9)
Myalgia	52	(24.6)
Headache	31	(14.6)
Diarrhea	6	(2.8)
Taste-smell loss	17	(8)
Asymptomatic	48	(18.5)
Presence of lung involvement in RT-PCR positive patients (n=259)	29	(11.2)

Table 2 Comparison of clinical characteristics and antibody levels of HCWs

	Elecsys® Anti-SARS-CoV-2 test		
	Negative	Positive	p value
	Mean (± SD)	**Mean (± SD)**	
Age, year	35.6 ± 8.3	36.2 ± 8.4	0.338*
	n (%)	**n (%)**	
Gender			
Female	245 (50.3)	242 (49.7)	0.236
Male	125 (55.1)	102 (44.9)	
Age Groups			
18-40	266 (52.7)	239 (47.3)	0.414
41-50	91 (51.4)	86 (48.6)	
>51	13 (40.6)	19 (59.4)	
Job groups			
Doctor	58 (54.7)	48 (45.3)	0.522
Nurse	212 (49.9)	213 (50.1)	
Medical secretary	60 (56.6)	46 (43.4)	
Laborant/Radiology technician	36 (54.5)	30 (45.5)	
Cleaning and support staff	4 (36.5)	7 (63.6)	
Risk groups according to the study area			
Low	60 (56.6)	46 (43.4)	0.556
Middle	40 (51.9)	37 (48.1)	
High	270 (50.8)	261 (49.2)	
At least one comorbid disease			
Absent	295 (50.9)	284 (49.1)	0.335
Presense	75 (55.6)	60 (44.4)	
RT-PCR history			
Negative	233 (51.2)	222 (48.8)	0.664
Positive	137 (52.9)	122 (47.1)	
Lung involvement during COVID-19			
Absent	137 (59.6)	93 (40.4)	< 0.001
Presense	0 (0)	29 (100)	
	Median (IQRs 25-75%)	**Median (IQRs 25-75%)**	
Days from PCR positivity to the day of antibody testing	101 (44- 131)	75.5 (43- 134)	0.426**

*p= Student's t-test
**p= Mann-Whitney U test
Other p values were calculated by the chi-square test.

The median value of the time elapsed between the date of RT-PCR positivity and antibody measurement of the participants was 82 days (IQRs: 43-132). The most common symptoms were cough (26.5%), myalgia (24.6%), weakness (18.9%), fever (16.1%), headache (14.6%) and asymptomatic (18.5%) (Table 1).

Table 1 shows the Demographic and clinical characteristics of the HCWs.

370 (51.8%) HCWs's the antibody level was negative, and 344 (48.2%) was positive. While 47.1% (n=122) of the HCWs with positive RT-PCR were antibody positive, 48.8% (n=222) were negative (Table 2).

The antibody levels of the participants in terms of mean age and age groups, there was no statistically significant difference (p values 0.338 and 0.414, respectively). Also, there was no statistically significant difference in antibody levels by gender (p=0.236). There was no significant difference between antibody positivity according to the presence of comorbidity and the risk groups (p=0.556, p=0.335, respectively) (Table 2).

According to job groups, although the highest seroprevalence was in cleaning and support personnel (63.6%), no significant correlation was found between antibody levels and occupation (p=0.522) (Table 2).

The history of RT-PCR positivity and the time elapsed since RT-PCR positivity was not significant by antibody positivity (p= 0.664, p=0.426, respectively). There was a statistically significant difference between lung involvement and antibody positivity during Covid-19 infection (p=<0.001). Antibody levels were positive in all HCWs (n=29) with lung involvement (Table 2).

Discussion

Covid-19 infection can manifest in different clinical pictures, including asymptomatic infection. Asymptomatic infection rates may vary in studies. In a systematic review, rates of asymptomatic infections ranged from 1.6% to 56.5% [5]. Approximately twenty percent of the HCWs had asymptomatic Covid-19 disease in our study.

A systematic review and meta-analysis study examined research published until August 2020, 47 studies covering 399265 people from 23 countries, SARS-CoV-2 seroprevalence in the general population ranges from 0.37% to 22.1%, with the pooled estimate reported as 3.38% [6]. In the study conducted in Boston in July 2020, there was a 5.5% IgG positivity, and 1.8% of people had mild Covid-19 symptoms, but they did not perform a test for diagnosis [7]. In the seroprevalence study conducted in the UK between May-June 2020 in HCWs, there was 31.6% antibody positivity [8]. In another survey conducted in April-May 2020, 1.6% SARS-CoV-2 seroprevalence was observed in 734 HCWs from 18 different centers [9]. In the study conducted in Belgium in April 2020, researchers measured IgG/IgM with the rapid test and found 6.4% IgG positivity in 3056 HCWs [10]. In our study, the seroprevalence of SARS-CoV-2 antibodies in HCWs was 48.2%. We can explain the high rate because our hospital serves as a tertiary level and the only pandemic hospital in the region.

The study at Hacettepe University between March and September 2020 showed a seropositivity rate of 7.4% of 774 HCWs. While seropositivity was 75.6% in HCWs diagnosed with COVID-19 by PCR or CT before the antibody test, this rate was 3.5% in HCWs not diagnosed with COVID-19 [11]. In a study conducted with 932 HCWs in three pandemic hospitals in Istanbul and Kocaeli in June 2020, seropositivity was 12.3%. The seropositivity HCWs who were previously diagnosed with PCR was 78.2%, while the rate was 2.7% in HCWs not diagnosed with COVID-19 [12]. Seroprevalence rates vary depending on factors such as the intensity of the pandemic region, working conditions of hospitals, date of the study. One reason for higher seroprevalence positivity than other studies is that our study was conducted later than others. The increased rate can be explained by the increase in HCWs encountering the Covid-19 infection.

Similar to other studies, we found no relationship between age, gender, and the presence of comorbidity in terms of SARS-CoV-2 antibody positivity [7,10,11].

When evaluated according to risk groups for the transmission of Covid-19 infection, in Mishra et al. [13], seropositivity was higher in the high-risk category. On the other hand, Hunter et al. [9] did not detect a difference between high and low contact risk groups. They attributed this to the effectiveness of personal protective equipment use. Alkurt et al. [12] found no difference between risk groups. In our study, there was no difference between risk groups, also.

Similar to our study, other studies have reported higher antibody seroprevalence rates in HCWs with lung involvement [11,12]. A higher rate suggests a positive correlation between disease severity and antibody positivity. Yan et al. [14], a positive correlation was observed between the severity of SARS-CoV-2 infection and IgG antibodies. The highest antibody levels were in the group of severe patients. Our study did not detect antibody positivity in 52.9% of HCWs with PCR positive, and 18.5% of those who had the disease were asymptomatic. Lower antibody formation may occur in HCWs with mild or asymptomatic infections.

The main limitation of our study was that we measured antibodies at one time period and did not assess the changes in antibody levels over time. Another limitation of our research, it was performed in a single center, and seroprevalence results can not generalize to the whole country.

Conclusion

Antibody tests can determine SARS-CoV-2 seroprevalence in the community or HCWs. We may explain the higher seroprevalence rate by 1) undiagnosed asymptomatic infections, 2) the rise in the number of people exposed to the virus as the pandemic continues, and 3) serious infections such as lung involvement. Multicenter studies with more participants would be helpful to determine overall seroprevalence rates.

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Metastatic tumor of the ciliary body manifesting as phacomorphic glaucoma: A clinical case

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Abstract

Introduction: Metastatic ciliary body tumor is a relatively rare tumor with a poor prognosis. Ciliary body tumors manifest as closed angle glaucoma, secondary glaucoma (phacomorphic glaucoma (PG), neovascular glaucoma), chronic uveitis, and cataract. The diverse manifestation of symptoms leads to diagnostic errors.

Case presentation: This article presents a clinical case of a man aged 59 years with PG of the left eye. Ultrasound biomicroscopy revealed: a mushroom-shaped mass on the ciliary body penetrating toward the posterior chamber, with indistinct boundaries. Metastatic tumor of ciliary body had clinical manifestation as PG in this patient.

Conclusion: All types of secondary glaucoma and acute attack of primary closed angle glaucoma should be carefully examined for intraocular tumor. Incorrect choice of treatment tactics for such patients can lead to common complications such as metastasis.

Key words: ocular metastases, phacomorphic glaucoma, ultrasound biomicroscopy

Introduction

Metastatic tumors are a rare cause of intraocular tumors and cases due to ciliary body neoplasia are rarely described in the literature. Malignant neoplasms of the breast, lung, mediastinum, and kidney are frequent causes of metastases to the eyeball [1,2]. According to Shields CL et al. tumors of other organs quite often give metastases to the iris (64 %), ciliary body (67 %), chorioid (1 %) and the disease is often accompanied by elevated intraocular pressure (IOP) [3].

When the ciliary body tumor reaches a large size, patients complain of visual impairment associated with lens deformity and dislocation. When the mass invades the angle of the anterior chamber (AC), IOP increases [4].

The treatment of glaucoma, due to metastases of malignant tumors of various localizations, is challenging. Since, drug therapy is varied and often has little efficacy. According to Radcliffe N.M. et al. the use of prostaglandin analogs increases uveoscleral outflow, and pilocarpine activates trabecular outflow, which in turn can increase the risk of malignant tumor metastasis [5]. Antiglaucomatous surgery is contraindicated due to the possibility of tumor cells entering the bloodstream and spreading hematogenously to other organs [6]. Treatment of ciliary body tumors includes local resection, enucleation, radiation therapy and laser treatment, and each case requires an individual approach [4,7].

The prognosis of visual function depends on the type of tumor and extent of ocular involvement, as well as the treatment received. The main goal of treating a neoplasm of the eyeball, is to control the tumor, then control IOP. Additionally, the treatment of any intraocular tumor should be done simultaneously with the oncologist.

In this article, we would like to share a clinical case of metastatic ciliary body tumor associated with phacomorphic glaucoma (PG).

Case presentation

The principles of the Declaration of Helsinki were followed in the article. A 59-year-old man, Asian nationality, presented to the emergency ophthalmology department of the Central City Clinical Hospital with the complaints of acute pain, redness, sharp decrease in vision in the left eye. The above complaints had been bothering him for one month. When the pain intensified, only then the patient went to an ophthalmologist at the

place of residence. The oculist in the outpatient clinic diagnosed PG in the left eye, provided appropriate care and referred the patient for inpatient treatment.

The life history: the patient had been on the dispensary registration since 2016 with an oncologist for surgical carcinoma of the thymus gland, metastases of the thymus gland (right thoracotomy, removal of formation S 3 of the upper lobe of the right lung). The patient refused radiation therapy after surgery and had not been seen by an oncologist for the last two years. He was registered with a general practitioner for arterial hypertension, grade III.

An examination of his visual acuity in the right eye equaled 0.8, not correct, in the left eye - 0.04, not correct. IOP in the right eye (Maklakov tonometer) was 18 mmHg, in the left eye - 47 mmHg.

On biomicroscopy the right eye is quiet. The cornea was clear. The depth of the anterior chamber was medium, the moisture was transparent. The pupil was rounded, 2.5 mm in diameter, pupil reaction to light is preserved. The iris is subatrophic, pigmentary border was thinning. The anterior cortical layers of the lens were irregularly clouding. Ocular fundus: Optic disk (OD) with clear borders and optic disc excavation (E/D) - 0,5. The retinal arteries were sharply narrowed, the veins were of irregular caliber, and there were grade II arteriovenous crosses. The ratio of artery to vein was 1:3. The macular reflex was smoothed.

Left eye: congestive injection of the eyeball. A slight edema of the corneal epithelium. Folds of the descemetal membrane were defined. The anterior chamber was shallow. The pupil was oval in shape, wide (4.5 mm in diameter), unresponsive to light. The iris was subatrophic and without pigmentary border. The lens was swollen, the anterior capsule is strained, and the

Figure 1 - In the light of the slit lamp of the left eye seen are corneal edema and swollen cataract (photo after decreasing of high intraocular pressure).

anterior cortical layers was cloudy. Details of the ocular fundus cannot be seen because of a cloudy lens (Figure 1).

On the gonioscopy of the right eye, the anterior chamber angle (ACA) was narrow, and the iris root was convex. Iris root penetrates into the anterior chamber, ciliary body stripe and scleral spur were not seen. Left eye: ACA was closed.

Ultrasound investigation of the right eye revealed the vitreous body destruction. There was a hyperechogenic shadow in the ciliary body area at 6 o'clock on the left eye. The axial length (AL) of the right eye was 22.70 mm, anterior chamber depth (ACD) - 2.73 mm, lens thickness - 5.01 mm. Left eye: AL-21.93 mm, PC - 1.95 mm, lens thickness - 5.26 mm.

Ultrasound biomicroscopy (UBM) of the left eye: ACD - 2.30 mm average, ACA closed, posterior chamber depth (PCD) 0.53 mm average, lens thickness 4.9 mm, cinnamic ligaments 0.38 mm, ciliary body hypertrophied; thickness at 3 o'clock 1.44 mm, at 6 o'clock 2.85 mm, iris root convex. At 6 o'clock, the cinnamic ligaments were absent and there was a subluxation of the lens due to the ciliary body. At 6 o'clock, "+" tissue of heterogeneous echogenic density with hyperechogenic margins toward the posterior chamber, margins indistinct, irregular shape, true size was impossible due to the depth of formation, maximum size in the visible zone was 2.85 mm (Figure 2-4).

Figure 2 - On ultrasound biomicroscopy of the left eye are seen metastasis to the ciliary body and subluxation of the lens.

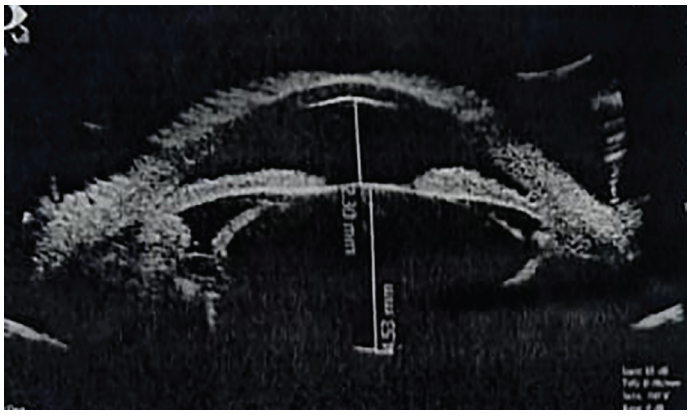


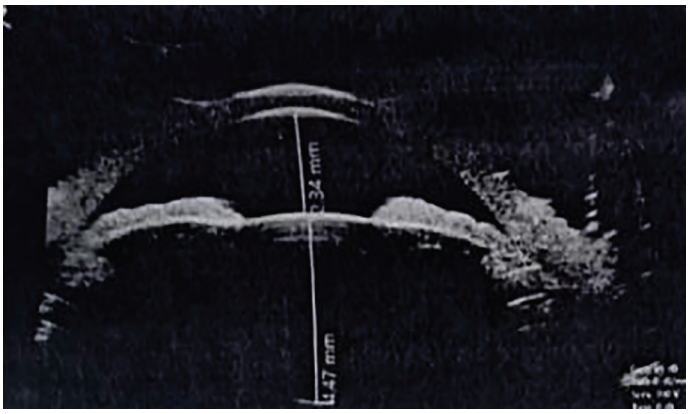
Figure 3 - Ultrasound biomicroscopy shows plus tissue of inhomogeneous echo density with irregular shape and hyperechoic density, the edges towards the posterior chamber are indistinct.

Figure 4 - Ultrasonic biomicroscopy picture in the area of tumor.

Given a life history of thymus gland carcinoma, the patient was referred for consultation to an oncologist, who identified metastases to the mediastinal lymph nodes and to supraclavicular lymph nodes. Results of chest-computed

UBM of right eye ACD was medium 2.34 mm, ACA was narrow, PCD is medium - 0.57 mm, the lens thickness - 4.47 mm, cinnamic ligaments were medium 0.53 mm, thickness of ciliary body was hyporrhotic (1.24 - 1.30 - 1.32 mm), iris profile is convex. The cinnamic ligaments were sharply thinned. The position of the lens is central. Pupillary preblock (Figure 5). The patient was diagnosed with OD - Age-related immature cataract after instrumental examination. Hypertensive retinal angiopathy. OS - Phacomorphic glaucoma. Ciliary body melanoma? Metastatic tumor of the ciliary body?

Figure 4 - Ultrasound biomicroscopy of the right eye, the angle of the anterior chamber is narrow.



tomography: condition after right thoracotomy, removal of a mass S 3 of the upper lobe of the right lung (2016). On computer tomography shown lymphoadenopathy of mediastinal, right supraclavicular lymph nodes. Ultrasound of peripheral lymph nodes: lymphoadenopathy of cervical, supraclavicular, axillary, and inguinal lymph nodes. Biopsy of supraclavicular lymph node on the right: the morphological picture corresponds to the metastasis of solid carcinoma to lymph nodes.

Radiotherapy and chemotherapy were recommended to the patient by the oncologist. Phacoemulsification of cataract with local resection of the ciliary body was recommended to the patient by us, but the patient refused the surgical treatment of his eye.

Discussion

Here, PG is caused by deformation and dislocation of the lens of the eyeball. According to Shields et al. [8], elevated IOP due to intraocular tumor accounts for 5% to 7.5% of cases. Ferry A.P. et al. believe that one of the frequent localizations of metastases in 81% of cases is the vasculature [1]. Metastases to the ciliary body are more often accompanied by lens displacement and sectoral cataract. In turn, iris metastases clinically manifest as uveitis with elevated IOP and pseudohypopyon [4]. Causes of increased IOP depend on the localization of choroidal metastases. Thus, according to Sheilds et al., based on a study of 2704 eyes of patients with intraocular neoplasms, found that 80% of cases of metastases near the iris root cause obstruction of the trabecular apparatus by detached tumor cells [4,9]. Iris neovascularization in chorioidal metastases, which can cause the closure of the ACA by reconfiguring the lens and aperture, have also been identified. In this study patients, the mechanism of increased IOP is due to displacement or increase in the thickness of the lens [4].

Small-sized ciliary body tumors need to be removed within healthy tissue. Consequently, larger tumors are treated with brachytherapy (suturing an applicator to the sclera over the tumor) or removal of the eyeball [10]. In practice, there is a combined treatment method as local ciliary body resection with phacoemulsification of the lens for small ciliary body tumors with cataract [10,11]. This method has advantages over radiotherapy, such as low recurrence and preservation of vision. After radiotherapy, the outcome can vary, including subatrophy of the eyeball and tumor recurrence [11]. Our patient was recommended the combined method described above, but the patient refused treatment.

Conclusion

Incorrect choice of treatment tactics for such patients can lead to common complications such as metastasis. Our case emphasizes that despite the rarity of metastatic ciliary body tumor, careful examination of the patient's visual organ is necessary to exclude a primary intraocular tumor as the cause of secondary hypertension.

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