TMSJ

TURKISH MEDICAL STUDENT JOURNAL

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Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL:http://www.cdc.gov/ncidodlElD/cid.htm.

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EDITORIAL

Dear readers,

I would like to present to you TMSJ's June issue of 2020. In this issue, you will find 7 articles, consisting of 4 original researches, 1 case report, and 2 reviews.

As all the people in the world, we are facing a pandemic, COVID-19. During this time, a lot of things have changed in our daily lives. COVID-19 has also affected the science world. Hundreds of articles have published about the pandemic and many science enthusiasts are working to better the conditions and trying to find an effective treatment and a vaccine for SARS CoV-2. During this pandemic, health care workers have devoted their selves to treat the patients infected with the virus. Words are not enough to show our appreciation and gratitude towards them. On behalf of the TMSJ editorial board, I would like to thank every member of the society who has worked hard to improve the living conditions nowadays.

Since today's medical students are future doctors, it is important for them to recognize the clinical features of COVID-19. Therefore, Çifcibaşı et al. have put great effort and presented an original research regarding the thoughts and awareness of medical students from 41 different universities of Turkey about the COVID-19 pandemic. I truly believe that this study put a light on for us to understand the attitudes of medical students in our country towards COVID-19.

In addition, Koçyiğit et al. prepared a very detailed review of COVID-19. I think, our readers would find this review worth reading. Since COVID-19 is very popular nowadays, it is important to reach rightful information.

Every year, the month of June is celebrated as Pride month. Various events are held in order to raise awareness of the current issues that the LGBT community faces. Akay et al. made a contribution to this issue of TMSJ with a multi-centered original research regarding the opinions and attitudes of medical students from different countries towards LGBTQIA+ individuals.

Nowadays, people are more tend to sedentary living. However, the importance of exercise and its effects cannot be denied. Mutlu et al. made a multi-centered research among medical students from different universities and evaluated the effects of physical exercise on low back pain which is very common in most of the students.

Vaccine hesitancy is identified by the WHO as one of the top ten global threats of 2019. In order to raise awareness about anti-vaccination, Koçak et al. made a research among medical, nursing, and pharmacy students who are going to be health care workers in the future. Koçak et al. evaluated the knowledge levels of students about vaccination and its safety.

Şenödeyici et al. presented a case regarding cervical meningocele in a newborn. Since neural tube defects are the most common congenital anomalies worldwide, it is important for our readers to be aware of it and how to approach to the patients.

Day by day, people are giving more attention to healthy nutrition. The effects of various vitamins to our metabolism is a very popular subject. Başpınar et al. prepared a review of the beneficial effects of vitamin K and osteocalcin on glucose metabolism.

I hope that in these days that we stay home, TMSJ' new issue will help you have a time full of science. I hope to meet our dearest readers in the next issue! Stay home, stay healthy!

Nur Gülce İŞKAN
Editor-in-Chief

CONTENTS

THOUGHTS AND AWARENESS OF MEDICAL STUDENTS ABOUT THE COVID-19 PANDEMIC

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ABSTRACT

Aims: This study aims to evaluate medical students' knowledge, thoughts, and awareness of the COVID-19 pandemic. ***Methods:*** A questionnaire consisting of 31 questions was prepared for this descriptive study. In the questionnaire, medical students' knowledge, attitudes and behaviors during the COVID-19 pandemic were investigated. Categorical variables are demonstrated as numbers and percentages, whereas continuous variables are presented as minimum, maximum, and mean values. ***Results:*** A total of 575 participants completed the questionnaire. The mean participant age was 21.7 years. Fifty-two percent of participants knew about the coronaviridae family before the outbreak and 38.8% were informed about COVID-19 in their medical schools. Of the students, 99.7% stated that the first case's origin was in China. Eighty percent of the participants stated that droplet spread is the transmission route of COVID-19. The most common opinion about the incubation period of the SARS CoV-2 was two to twelve days. Being older than 65 years old, having a comorbidity, being immunosuppressed, or working in the healthcare sector were the most particular risk factors to get infected. The majority of the participants follow the vaccine developments from social media, radio and television. According to 75.83% of the participants, all people should wear a mask in daily life for protection. ***Conclusion:*** The epidemiology and diagnostic factors of COVID-19 are well known by medical students. To minimize information pollution and raise awareness, medical students should be educated about pandemic and management of it. Further evaluation with various methods and more participants may help to better understand the awareness of the COVID-19 pandemic in medical students. ***Keywords:*** COVID-19, SARS CoV-2, medical student, pandemic

INTRODUCTION

Ever since the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002, a large number of SARS related coronaviruses (SARS-CoV) have been discovered (1). In December 2019, pneumonia with an unknown etiology was detected in China (2). On January 3rd, 2020, 44 patients with pneumonia of unknown etiology have been reported to the World Health Organization (WHO) by the national authorities in China (2). The following researches detected that it was a new type of SARS CoV-2. The origin of Coronavirus Disease-19 (COVID-19) was traced back to an animal market in Wuhan, China (1). On 30 January 2020, COVID-19 has been declared as the sixth public health emergency of international concern by the WHO (3). According to the WHO's official website, more than 3 million SARS CoV-2 cases and 243 thousand of deaths by SARS CoV-2 have been reported around the globe (as of 6 May 2020). Epidemiologic and retrospective researches found that people older than the age of 65 and people who are either immunosuppressed, pregnant, or chronically ill are at a greater risk of morbidity and mortality than other groups (4).

The virus encodes 4 different proteins that allow it to attach to the surface of the human cells and enter the cell via the human angiotensin-converting enzyme, whereafter the interaction starts a cytokine storm to bring out the symptoms (5). The main symptoms that patients contracted with COVID-19 are dry cough, fever, and tiredness. Other symptoms include shortness of breath, sputum production, myalgia, sore throat, and headache (6). Centers for Disease Control and Prevention (CDC) announced that some symptoms of COVID-19 require immediate medical attention (7). The patients having difficulty in breathing, persistent pain in the chest, bluish lips, or inability to arouse are encouraged to seek urgent medical intervention. Most of the time, symptoms do not appear in the first 2 days of exposure. The incubation period of COVID-19 is estimated to be between 2-14 days. However, an article published in JAMA reported a case with an incubation period of 19 days (8).

Coronaviruses can spread through ingestion or inhalation of respiratory droplets that are released to the environment by coughing or sneezing, or through contact with infected surfaces (9).

Currently, there are different diagnostic methods used in COVID-19: most prominent methods are reverse transcription-polymerase chain reaction (RT-PCR) and computed tomography (CT) scans (10). Although some studies suggest that oropharyngeal swabs can also be used in sample collection (11), the CDC recommends the usage of nasopharyngeal swabs (12). The collected samples are stored in 2-8°C for up to 72 hours before they are sent to be analyzed further. CT scans are not directly used as a diagnostic tool because of the high rate of misdiagnosis. Patients are diagnosed with ground glass opacities, interlobular septal thickening, and air bronchogram signs. A study by Li et al (13). reported that 88% of 919 patients had multiple lesions in both of the lungs with ground-glass opacities. Overall, the new coronavirus disease is usually diagnosed by RT-PCR and CT scans (14).

The virus can be isolated from many animals, but bats are accepted as the major natural coronavirus reservoir (15). Several studies found that animals, especially domestic animals (including pets) can be infected with the virus (15).

Medical staff has always been at risk of infective diseases because of the fact that they are in close contact with patients. As we know, COVID-19 can also transmitted from asymptomatic patients and this is multiplying the risk of getting infected (16). One patient in Wuhan who would undergo surgery had infected 14 health care workers which 12 of them was in close contact (17). These kinds of events and cases and the fact that we do not know much about COVID-19 are making the situation riskier and more stressful. We should not be forgetting the fact that medical students are also in close contact with patients too. Thus, having the true and enough knowledge about the pandemic process and the virus itself is important to their actions because with this way they can overcome the stress. Therefore, they are also at risk for infectious diseases. Even though The American Association of Medical Colleges (AAMC) advised medical schools to not to involve medical students in patient care (18, 19), some schools in the US and in Europe graduated their final-year medical students early because of workforce shortage (20) and some volunteer medical student teams were formed (21).

Keeping in mind that today's medical students are the foundation of the future healthcare system, it is important to assess their knowledge on COVID-19 as an example for future pandemics and public health safety issues. In one of the studies about COVID-19 knowledge among the Iranian medical students (5th-7th year), they found that the knowledge of the students is on a high level (21). These results are giving feedback about the worries which is the knowledge and stresses among the future health care workers. Despite the high level of knowledge about COVID-19 among Iranian medical students who participated in the study, self reported preventive behavior does not seem as good. This kind of information about the medical students can let us see country's future health systems. We also want to exa-

mine Turkish medical students' knowledge during this pandemic period. This study aims to evaluate the knowledge, thoughts and awareness of medical students about the COVID-19 pandemic.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Acıbadem University Medical Faculty (Protocol Code: ATADEK 2020-05/40). This descriptive study was carried out between April and May 2020. Individuals other than medical students were not included in the study. The study was conducted via a self-administrative online questionnaire in the Turkish language and delivered through scientific research communities of the medical schools. The participants were informed and their consent for participation was taken at the beginning of the questionnaire.

The questionnaire was prepared via Google Forms and consisted of 31 questions and five distinct sections. The first section contains the informed consent. The second section consisted of demographic questions: date of birth, gender, current year in university, and the name of the university. The third section was designed to assess the knowledge level of the participants on the COVID-19 pandemic. This section consisted of 14 questions (questions 5th-18th). The fourth and fifth sections were designed to investigate the attitude and behaviors of the students towards/during the pandemic. Section four consisted of 9 questions (questions 19th-27th) and the fifth section consisted of 4 questions (questions 28th-31nd). In the 3rd and 4th sections, checkboxes and multiple-choice questions were utilized; in the 5th section, linear scale questions were used.

Categorical variables are demonstrated as numbers and percentages, whereas continuous variables are presented as the minimum, maximum, and mean values. The IBM SPSS version 23 was used for the presentation of the data.

RESULTS

A total of 575 participants completed the questionnaire. The mean participant age was 21.7 ± 1.9 years (range: 17-33 years). Three hundred and eighty-three (66.6%) participants were female, 190 (33%) were male, and 2 (0.3%) did not declare their gender. All participants were undergraduate medical students. The distribution of grades is shown in Table 1. Students from 41 different universities participated in the questionnaire. The highest participation was from Trakya University with a rate of 31.3%.

According to questions, 301 (52.3%) participants knew about the coronaviridae family before the outbreak, and 223 (38.8%) were informed about COVID-19 by their universities. Five hundred and seventy-three (99.7%) students stated that the origin of the pandemic was China. Of the participants, 80% stated that droplet spread is the transmission route of COVID-19 (Table 2). When participants' opinion about the animal to human transmission was asked 310 (53.9%) students chose "transmittable" for this question, 174 (30.3%) chose "not transmittable" and 91 (15.8%) chose "I don't have any idea". In addition, human to pet transmission was not accepted by almost half of the participants [255 (44.3%)] and 90 (15.7%) participants didn't have any idea. Being older than 65 years old, having a comorbidity, being immunosuppressed or working in the healthcare sector were the most selected groups with the highest mortality and morbidity risk (Table 3). The most common opinion about the incubation period of SARS CoV-2 was 2 – 14 days (Table 4). Dry cough, high fever, and difficulty in breathing or shortness of breath were the main symptoms of SARS CoV-2 according to participants (Table 5). Distributions of answers to symptoms that require the emergency intervention of COVID-19 according to CDC are presented in Table 6. Answers to the epidemiologic history criteria are detailed in Table 7. General opinions about the parameters that are used to investigate COVID-19 diagnosis can be seen in Table 8. Nasopharyngeal swab (58.96%) followed by oropharyngeal swab (53.39%) were the most common answers to the question of which clinical samples can be used in the diagnosis (Table 9). Distribution of answers to the question about the importance of social isolation is detailed is detailed in Table 10.

More than half of the participants follow vaccine developments from social media [341 (59.30%)], radio and television (45.36%) (Table 11). Mask, gloves, cologne, and alcohol-based antiseptic solutions were the most common items used by students as a precaution (Table 12). According to 75.83% of the participants, all people should wear a mask in daily life (Table 13). Almost half of the participants wash their hands with water and soap 5-9 times a day and they spend 10-19 seconds per wash (Table 14-15). During the COVID-19 pandemic period, 56.0% of participants think that interns can be called for duty in a state of emergency. The most common lack of healthcare professionals working in Turkey during the COVID-19 pandemic was personal protective equipment (57.0%) according to participants (Table 16). Of the participants, 38.1% thought that they had a maximum of 20.0% risk of getting infected (Table 17). The most common answer (28.0%) to the risk of a family

member being infected was between 20-40% (Table 18).

Information pollution related to the pandemic, the social responsibility awareness of the student from the first case in Turkey, the disruption level of medical education was scored in the questionnaire. Whether there was a change in the departments they were planning to choose in specialization was questioned. The average score and standard deviation of the answers described in Table 19.

Table 1: Medical school grades' dispersion of the participants.

Grade	Number	Percentage (%)
Preparatory	1	0.17
1	191	33.21
2	128	22.26
3	102	17.73
4	59	10.26
5	74	12.86
6	20	3.47
Total	575	100

Table 2: Responses for the transmission route of the SARS CoV-2.

Route of Transmission	Number	Percentage (%)
Droplet Spread	460	80
Airborne	60	10.4
Direct Contact	43	7.5
Oral	7	1.2
Faecal–oral	4	0.7
I don't have any idea	1	0.2
Total	575	100

Table 3: Responses for the criteria to be in risk group for COVID-19.

Risk Group	Number	Percentage (%)
65+ age (year)	486	84.52
Comorbidity	485	84.35
Immunosuppressed patients	451	78.43
Healthcare workers	350	60.87
55-64 age (year)	209	36.35
Pregnant women	202	35.13
All of them	81	14.09
45-54 age (year)	54	9.39
0-19 age (year)	27	4.7
Other	16	2.78
20-44 age (year)	10	1.74
I don't have any idea	1	0.17
Total	575	100

(Participants were able to choose more than one option.)

Table 4: Responses for the incubation period of SARS CoV-2 (days).

Incubation Period	Number	Percentage (%)
0-1	1	0.2
2-14	520	90.4
15-21	23	4
I don't have any idea	31	5.4
Total	575	100

Table 5: Responses for the main symptoms of COVID-19.

Main Symptoms	Number	Percentage (%)
Having difficulty in breathing or shortness	529	92
High fever	521	90.61
Dry cough	499	86.78
Persistent pain or pressure in the chest	230	40
New confusion	79	13.74
Bluish lips or face	53	9.22
All of them	35	6.09
Sputum cough	31	5.39
Other	16	2.78
Total	575	100

(Participants were able to choose more than one option.)

Table 6: Responses for emergency symptoms of COVID-19.

Emergency Symptoms	Number	Percentage (%)
Having difficulty in breathing or shortness	494	85.91
Chronic fever	293	50.96
Persistent pain or pressure in the chest	205	35.65
New confusion	161	28
Bluish lips or face	155	26.96
Dry cough	86	14.96
I don't have any idea	44	7.65
All of them	13	2.26
Sputum cough	10	1.74
Other	4	0.7
Total	575	100

(Participants were able to choose more than one option.)

Table 7: Responses for epidemiologic history of COVID-19

Epidemiologic History	Number	Percentage (%)
All of them	430	74.78
Contact with a COVID-19 positive case	137	23.83
Travel to risky areas	132	22.96
Fever or respiratory tract symptoms and contact with a case came from a risky area	126	21.91
Contact with a case came from a risky area and 2 or more cases with fever/ respiratory tract symptoms in the close area (school, family, work etc.)	91	15.83
I don't have any idea	4	0.7
Other	1	0.17
Total	575	100

(Participants were able to choose more than one option.)

Table 8: Responses for the diagnostic parameters of COVID-19.

Diagnostic Parameters	Number	Percentage (%)
All of them	268	46.61
Clinical findings	260	45.22
Contact with a person with COVID-19 suspicion	251	43.65
PCR	223	38.78
Radiological examinations like tomography	175	30.43
Blood examinations like complete blood count, CRP	72	12.52
I don't have any idea	13	2.26
Other	1	0.17
Total	575	100

(Participants were able to choose more than one option.)

Table 9: Responses for the test samples of COVID-19.

Test Samples	Number	Percentage (%)
Nasopharyngeal swab	339	58.96
Oropharyngeal swab	307	53.39
Bronchoalveolar lavage	187	32.52
Phlegm	143	24.87
Tracheal aspiration	139	24.17
Nasopharyngeal wash/aspiration or nasal aspiration	136	23.65
I don't have any idea	119	20.7
All of them	38	6.61
Stool	18	3.13
Other	3	0.52
Total	575	100

(Participants were able to choose more than one option.)

Table 10: Responses for the importance of social isolation.

Social Isolation	Number	Percentage (%)
All of them	388	67.48
To prevent older people and people with chronic diseases from getting infected	159	27.65
To prevent healthy people from getting infected	128	22.26
To decrease the workload of healthcare centers	120	20.87
I don't have any idea	5	0.87
Other	3	0.52
Total	575	100

(Participants were able to choose more than one option.)

Table 11: Responses for following vaccine development.

Following Vaccine Development	Number	Percentage (%)
Social media	341	59.30
Radio and television	261	45.39
Popular science platforms	199	34.61
Scientific studies or meetings	154	26.78
I don't follow	100	17.39
Other	12	2.09
Total	575	100

(Participants were able to choose more than one option.)

Table 12: Precautions that the students take for themselves or the people around them.

Precautions	Number	Percentage (%)
Social isolation	410	71.3
Mask	369	64.17
Home ventilation	349	60.7
Cologne	332	57.74
Alcohol based antiseptic solutions	218	37.91
Gloves	214	37.22
All of them	156	27.13
Other	1	0.17
Total	575	100

(Participants were able to choose more than one option.)

Table 13: The distribution of answers to the question regarding the people who need to wear a mask in daily life.

People Who Need to Wear a Mask	Number	Percentage (%)
All people	436	75.83
Sick people	133	23.13
People with suspected disease	131	22.78
People in contact with sick people	121	21.04
Healthy people	15	2.61
Other	5	0.87
Total	575	100

(Participants were able to choose more than one option.)

Table 14: Daily frequency of hand-washing.

Daily Frequency of Hand-Washing	Number	Percentage (%)
0-4	62	10.78
5-9	269	46.78
10-14	189	32.86
15+	55	9.56
Total	575	100

Table 15: The average hand-washing times of the participants.

Average Hand-Washing Time (s)	Number	Percentage (%)
0-9	28	4.9
10-19	271	47.1
20-39	255	44.3
40-59	15	2.6
60+	6	1.0
Total	575	100

Table 16: The greatest lack of healthcare professionals.

Lack	Number	Percentage (%)
Personal protective equipment	328	57
Materials to treat patients, such as medication or ventilator	67	11.7
Motivation	67	11.7
No lack	72	12.5
Other	41	7.1
Total	575	100

Table 17: Perception of self-risk of being infected in current pandemic period.

Percentage of Risk (%)	Number	Percentage (%)
0-20	219	38.1
21-40	169	29.4
41-60	121	21
61-80	40	7
81-100	26	4.5
Total	575	100

Table 18: Perception of the risk of a family member being infected in current pandemic period.

Percentage of Risk (%)	Number	Percentage (%)
0-20	219	38.1
21-40	169	29.4
41-60	121	21
61-80	40	7
81-100	26	4.5
Total	575	100

Table 19: *The average score and standart deviation of lineer scale questions.*

Questions	Minimum-Maximum	Average Score	Standart Deviation
Information accuracy about the pandemic	1-5	3.98	0.96
The social responsibility awareness expected to occur from the first case in Turkey	1-5	3.82	1.21
Disruption level of medical education	1-5	4.64	0.73
Change in the department of the speciality planned	1-5	2.43	1.46

(Rated 1 to 5.)

DISCUSSION

Since the COVID-19 outbreak in December 2019, there has been a great concern among all the people in the world. The knowledge of and attitudes towards infectious diseases are very important for the health and safety of students (22). As healthcare workers, medical students are at higher risk for infectious diseases as well (23). In the future, in case of an epidemic/pandemic, today's medical students will be the healthcare professionals who are responsible for the care of the general public. Therefore, it is important to determine their knowledge, thoughts, and awareness about the COVID-19 pandemic.

In this study, 575 medical students from different medical schools in Turkey filled out an online survey, and results were evaluated descriptively. In our study, 52.3% of medical students who participated in this questionnaire had knowledge of coronaviridae family before the COVID-19 pandemic and 38.8 % were informed about the COVID-19 in their faculties. Similarly, Taghrir et al. (21) reported that 43.3% of medical students received education about COVID-19. These rates show that the majority of medical students have not been trained about COVID-19. Although most medical students may not be trained on this subject,

99.7% of the students stated that the first case was seen in China. In the study of Taghrir et al. (21), this rate was 91.7% which was lower than our study. COVID-19 was first detected in China presented as atypical pneumonia in December 2019 (2). It may mean that, in the pandemic period we live in, the vast majority of medical students are informed by their own means. Eighty percent of students stated that the droplet spread is the main transmission route, which was lower than Iranian medical students (21). COVID-19 is a viral infection that can spread through ingestion or inhalation of respiratory droplets (9). Of the students, 53.9% stated that SARS-CoV-2 can be transmitted from an infected animal to a non-infected person and 40% stated that it can be transmitted from an infected person to a non-infected pet. SARS-CoV-2 is thought to be primarily transmitted from bats to humans and is transmitted from person to person (24). There are not many studies or case reports indicating that the virus is transmitted from human to animal. However, the first case seen in an animal was the tiger in a zoo in the United States and the test was positive for SARS CoV-2 (25). Until this time, 2 dogs and 2 domestic cats have tested positive for SARS CoV-2. The common feature of these animals is that they live with infected owners (26).

Identifying the risk groups for COVID-19 is important to manage the outbreak and to take preventive measures. Although there are many guidelines suggesting different risk groups for the disease, they agree on the major ones such as 65+ age (year), comorbidities and immunosuppressed patients (27-29). The National Health Service (NHS) suggests two risk group categories: high risk (clinically extremely vulnerable) and moderate risk (clinically vulnerable) (27). The NHS includes people who are pregnant in the moderate risk group although a study done by Zhang et al. (29) reported the neonates of the infected women did not carry the SARS-CoV-2 infection. The prognosis for pregnant women was indifferent to the general public (29). Despite the different approaches, the medical students who participated in our study have a good level of knowledge according to their answers: 84.52% for people older than 65 years, 84.35% people with comorbidities, and 78.43% for immunosuppressed people being the most common risk groups.

The incubation period of SARS-CoV-2 is 2-14 days (29-31). However, an article published in JAMA reported a case with an incubation period of 19 days (8). 90.4% of the participants answered the question in accordance with the literature.

The main symptoms of COVID-19 are fever, cough, dyspnea, and headache (7, 32, 33). The participants showed good knowledge; 92% for dyspnea, 90.61% for high fever, and 86.78% for coughing. Nevertheless, there are many atypical symptoms to the SARS-CoV-2 infection and a certain percentage of the patients are asymptomatic and diagnosed via screening protocols (32-34). According to the study done by Kong et al. (32), asymptomatic patients had similar comorbidity ratios, but they were younger.

Emergency symptoms listed on CDC are trouble in breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, and bluish lips or face (7). The participants' answers; 85.91% for dyspnea, 50.96% for high fever, and 35.65% for chest pain showed that they were somewhat aware of the emergency symptoms. People who experience any of the emergency symptoms are recommended to seek medical care as soon as possible and the guidance of medical students can play a role in timely referrals (7). Turkish Ministry of Health's guideline states a detailed patient history including travel to risky areas, contact with a COVID-19 positive case, fever or respiratory tract symptoms should be taken from potential COVID-19 patients (35). The Ministry of Health also developed an app called "Hayat Eve Sığar" (HES) (Stay at Home) which uses mobile phone signals to track possible contact with COVID-19 positive cases and inform the users of high-risk areas (36). The joint effort of the Ministry of Health and the media might be the reason that 74.78% of the participants answered in accordance with the guidelines.

Molecular assay testing is the accepted method of diagnosis for COVID-19 (36-38). Li et al. (38) showed that chest CT can be helpful as a rapid diagnostic method combined with patient history and clinical examination although the molecular assay is currently the only accepted method for the confirmation of the disease (39). The answers correlate with the literature; 91.83% said clinical findings, 85.39% said PCR, and 77.04% said radiological investigations such as CT scan would be helpful in the diagnosis.

The CDC guideline recommends the specimen to be collected by a healthcare provider from the nasopharynx or oropharynx (40). Participants answered in accordance with the guideline with 58.96% saying nasopharynx and 53.39% saying oropharynx. However, a study performed by Gu et al. (41) showed the virus could be isolated from the stool of a patient even after they are released from the hospital. 3.13% of the participants said a stool sample could be used in the diagnosis. On April 21st, the FDA authorized the first test with at-home sample collection which also allows the nasopharynx or oropharynx sampling (41).

Various limitations have been forced on society to contain the spread of the infection. Individuals are compelled to remain at home and to isolate socially (42). According to our results, the importance of social isolation is unignorable. 27.65% of the students think that social isolation is necessary to prevent older people and people with chronic diseases to get infected. While 128 students thought it was important to prevent healthy people from becoming infected, 120 students said it was important to reduce the workload of health institutions. The reason that the number of students who choose these options is very close, maybe due to the linear relationship between the workload of the health system and the infected people.

COVID-19 can be transmitted from infected people without symptoms and its ability to cause a pandemic in a couple of months suggests that control of it will be hard without a vaccine (43). Therefore, we asked medical students if they are following anything about vaccine development. 261 of medical students are following vaccine development via radio and television, while 341 of them are following only via social media. There are 100 students who do not follow any development.

This shows us that social media is an important way to be up to date among medical students.

Ağalar et al. (44) stated that patients should wear masks during the whole time they are at the hospital and there should be hand sanitizers at the hospital entrance, waiting rooms, etc. Considering the importance of precautions such as wearing masks and gloves, using alcohol-based antiseptic solutions and cologne, home ventilation, social isolation, 156 of the students stated that they had all of the precautions listed on the questionnaire. 410 students only isolated themselves. Because its easy to implement, social isolation is the most preferred precaution.

Four hundred thirty-six medical students think that all people should wear masks. Wearing medical masks could reduce infection risk by 30% (45). This indicates that most of the medical students are aware of the benefit of wearing a mask. 269 students out of 575 reported that they are washing their hands 5 to 9 times in a day. It takes 10-19 seconds to wash hands for 47.1% of the students, also for 44.3% of the students, washing hands takes 20-39 seconds. An average recomended time to wash hands is 20 seconds (46). Compared to our study, it can be said that most medical students know how long they should wash their hands. In addition, 56% of students think that only intern doctors should be called back to school in case of an emergency. It is thought that intern doctors are competent among medical students.

According to 57% of participants, the greatest lack of healthcare professionals working in Turkey during the COVID-19 pandemic period is personal protective equipments such as masks, gloves, and safety goggles. Given that all protective equipment come via a chain of events, it is a known fact that the COVID-19 pandemic has disrupted the healthcare supply chain worldwide with shortages of raw materials and dramatic increases in prices (47). 11.7% of participants were worried if healthcare professionals had enough materials such as medication or ventilators necessary for the treatment of COVID-19 patients. Only 12.5% of participants thought that healthcare professionals lacked nothing, but this number is the minority. Interestingly, the participants were not as concerned about getting infected as they were of healthcare equipment. 38.1% of participants think the risk of themselves being infected is only 0-20%. Only 4.5% of the patients thought their risk of being infected was 81-100%, but this ratio increased to 8% when they were asked about the risk of a family member being infected. This data suggests that the students are more concerned about their family members' health. This might be due to the fact that family members go to work and the work environment could be risky. Besides, the students might be concerned if their family members are as careful as them by taking the necessary precautions against the virus. A reason for this might be that college students, who are very exposed to social media were cognizant of all aspects of the COVID-19 pandemic, and therefore the majority had many concerns (48). All the participants of our survey were medical students, therefore different results might have been obtained from students studying another major. There is a significant data that health education specifically aimed at improving knowledge of COVID-19 can help them maintain an optimistic attitude (49). Since our participants might have known about COVID-19 more than an average person, their concern levels might have been different. On a scale of 1 to 5, the participants rated their thoughts on information pollution during the pandemic as an average of 3.98. Bastani et al. (49) suggests that increased demand for information during the crisis, the easiness of information dissemination via social networks, marketing incentives, and the poor legal supervision of online content are the main reasons for misinformation dissemination. The study explains "disease statistics, treatments, vaccines and medicines; prevention and protection methods; dietary recommendations and disease transmission ways are the main subjective categories of releasing misinformation in regard to novel coronavirus outbreak" (49). It is important to remember that misinformation dissemination regarding disease causes psychosocial consequences; anxiety and depression during the pandemic lead to somatic symptoms that in turn cause significant physical and mental discomfort (48).

Although many think that they received incorrect information sometimes, they rated their social responsibility awareness from the first case in Turkey an average of 3.82. The participants, who are all medical school students, scored their disruption level of medical education during the pandemic as 4.64. As Ferrel et al. (50) explains, the irreplaceable value of attending class in-person was hard to replicate in online forums, especially for medical students. When the participants were asked whether there was a change in the departments they were planning to choose in specialization, the rate was 2.43. This indicated that the majority of students did not have any particular interest change during the pandemic.

In our study, there were some significant limitations. One of them was that the questionnaire we conducted to students is online. With the online questionnaire, some marking problems have occurred. One of our other limitations was to deliver the survey to students. Therefore, further studies with more participants are needed in this regard.

In conclusion, the epidemiology and diagnostic factors of COVID-19 are mostly well known by the medical students. To minimize information pollution and raise awareness, medical students should be educated about pandemic and management of it. Further experiments with various methods and more participants are needed to better understand the awareness of the COVID-19 pandemic.

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ASSESSMENT OF THE OPINIONS AND ATTITUDES OF MEDICAL STUDENTS TOWARDS LGBTQIA+ INDIVIDUALS

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ABSTRACT

Aims: The aim of this multicentral study is to analyze the opinions and attitudes of medical students towards lesbian, gay, bisexual, transgender, queer, intersex, and asexual individuals. **Methods:** A total of 1116 medical students from 59 universities in Turkey, 1 from Bosnia and Herzegovina, and 7 universities from Germany have participated in this study. The questionnaire consisted of 23 multiple-choice questions and an open-ended question. Data about the comparison of 1st and 6th year medical students were analyzed using the Pearson Chi-Squared test and the Fisher Exact test in IBM SPSS version 23.0.00. **Results:** The mean age of the participants was 21.2 ± 2.1 years (range: 17-34 years). There were 693 female, 417 male, 3 nonbinary, and 1 queer participants, and two did not declare their gender. There were 263 (23.6%) 1st year, 315 (28.3%) 2nd year, 179 (16.0%) 3rd year, 112 (10.0%) 4th year, 98 (8.8%) 5th year, and 139 (12.5%) 6th year students. There were 10 (0.9%) missing data. In the 15th question asking whether LGBTQIA+ individuals have the right to adoption or not, the 18th question asking if their school is providing education on sexual health, the 19th question asking if they consider themselves educated about safe sexual intercourse as an individual, and the 22nd question asking if they think that LGBTQIA+ individuals are more prone to catching sexually transmitted diseases, there were a significant difference between 1st graders and 6th graders. **Conclusion:** PIn conclusion, though the majority of answers given indicate a positive approach towards LGBTQIA+ individuals, it can be stated that the attitude of medical students towards LGBTQIA+ individuals is by far suboptimal. **Keywords:** Medical student, sexual orientation, gender identity, LGBTQIA+

INTRODUCTION

What exactly causes a person's sexual orientation and gender identity still has an ambiguous background. There has been a growing number of studies in recent years concerning the genetic nature of lesbians, gays, bisexuals, transgenders, queers, intersexes, and asexuals (LGBTQIA+) with great attention on the possibility of genetic origins (1). It was considered a psychological disorder for many years. The turning point of LGBTQIA+ history was when homosexuality was removed as a diagnostic category by the American Psychiatric Association in 1973 (2). It was then completely removed from the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980 (2, 3). However, bias opinions are still present within professionals about how the LGBTQIA+ population should be considered in society (4). The attitudes physicians present are important due to the crucial role they play in society. Health care differences related to the LGBTQIA+ po-

pulations are drawing more attention to the medical community. Health issues affecting the LGBTQIA+ population have been neglected and faintly studied throughout history (5, 6).

Patients of LGBTQIA+ community may present a challenge for physicians due to the high rates of psychiatric disorders, unreported domestic violence, substance abuse, and attempts of suicide which have been associated with the health care differences that are linked to social stigma, discrimination, and denial of human rights within the LGBTQIA+ population (7). LGBTQIA+ individuals often receive standard care, but may also be denied for care due to their sexual orientation or gender identity when compared to non-LGBTQIA+ patients (8). Furthermore, many health care professionals believe they are untrained or unprepared to care for LGBTQIA+ patients, and that differences in their treatment exist (9). Medical schools may present a great opportunity in reducing this gap with an early exposure to an environment that will include diverse patients along with different opinions, attitudes, and behaviors (10). Evidence also proves that LGBTQIA+ patients may be uncomfortable admitting their sexual orientation to physicians in fear of unfair treatment (11). This lack of disclosure may lead to a poor relationship between the patient and the physician. Consequently, the likelihood for an LGBTQIA+ patient to be treated wrongfully is significantly higher (12).

This multicentral study aims to analyze the different opinions and attitudes of medical students towards LGBTQIA+ individuals.

MATERIAL AND METHODS

Our multicentral, observational, and questionnaire-based study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2019/355). The research was carried out between April and May 15th, 2020. The questionnaire was sent to the students through each university's Scientific Research Society and European Medical Students' Association (EMSA). The study population was composed of undergraduate medical students. A total of 1116 medical students from 59 universities in Turkey, 1 from Bosnia and Herzegovina, and 7 universities from Germany have participated in the research. The questionnaire was conducted via Google Forms and included an informed consent section.

The questionnaire consisted of 24 questions. Multiple-choice questions and an open-ended question were used. In the questionnaire, sociodemographic data such as gender, age, school, grade, sexual orientation, and incline towards religion as well as their view on LGBTQIA+ community personally and as a future medical professional were questioned. The overall questionnaire is shown in Table 1.

The data were analyzed with IBM SPSS version 23.0.00. Categorical data (grade, school, sexual orientation, and gender identity together with the answers given) were stated as numbers and percentages. Continuous data (age) were stated as mean, standard deviation and range. Data about the comparison of 1st and 6th year medical students were analyzed using the Chi-Squared test, Pearson Chi-Squared test, and the Fisher Exact test. A p-value <0.05 was set for statistical significance.

RESULTS

This questionnaire-based study was conducted among 1116 medical students. The average of the participants' age was 21.2 years (standard deviation [SD]: 2.145 years, range: 17-34 years). The gender range of the participants is as follows: 693 females, 417 males, 3 non-binaries and 1 queer. Two of them did not declare their gender. Ten participants did not declare their grades. The distribution of grades is shown in Table 2.

Forty students (3.6%) from Bosnia and Herzegovina, 41 (3.8%) students from Germany, and 1035 (92.6) students from Turkey have participated in the research. There were 11 (%1) missing data.

Three hundred and ninety-seven (35.6 %) of the students identified themselves as religious and 718 (64.3 %) of them as non-religious. There was 1 (0.1 %) missing data. The participants were asked what their sexual orientations were, and their answers are shown in Table 3.

The 7th question was asking whether they had a friend or a family member from the LGBTQIA+ community. Out of 1116 participants, 639 (57.3%) of them stated that they had whereas 476 (42.7 %) of them stated that they did not, there was 1 (0.1%) missing data. While 1001 (89.7 %) of the participants said that they would accept an LGBTQIA+ individual as a friend, 114 (10.2%) answered that they would not. There was 1 (0.1%) missing data. Two hundred and fifty-seven (23.0%) students thought LGBTQIA+ individuals are psychologically ill and needed therapy, 856 (76.7%) of them did not. There were 3 (0.3%) missing data.

Eight hundred and eighty-two (79.0%) students stated that it would have been beneficial for our society to accept LGBTQIA+ individuals as "normal", while 232 (20.8%) of them stated that it would not. There were 2 (0.2%) missing data.

Table 1: The questionnaire used in this study.

Questions	Answers
1) Gender	
2) Age	
3) Which school are you currently enrolled in?	
4) What year are you currently enrolled in?	
5) Do you consider yourself a religious person?	Yes / No
6) What is your sexual orientation?	Heterosexual / Homosexual / Bisexual / Asexual / Other / I do not prefer to specify / Other
7) Is there someone who is LGBTQIA+ among your friends, relatives or people around you?	Yes / No
8) Would you accept an LGBTQIA+ individual as your friend?	Yes / No
9) Do you think LGBTQIA+ people have psychological disorders and need therapy?	Yes / No
10) Do you think that accepting LGBTQIA+ individuals as "normal" will benefit our society?	Yes / No
11) Do you find it appropriate to allow LGBTQIA+ individuals to work with children?	Yes / No
12) Do you think LGBTQIA+ individuals are mistreated in your society?	Yes / No
13) Do you think LGBTQIA+ individuals should be fully accepted in our society?	Yes / No
14) Do you think LGBTQIA+ individuals have the right to get married?	Yes / No / Other
15) Do you think LGBTQIA+ individuals should have the right to adopt?	Yes / No / Other
16) Does same-sex marriage endanger the ideology of a family?	Yes / No / Other
17) What are the sexual behaviours of LGBTQIA+ individuals according to your own opinion? (You can select one or more options.)	Same as heterosexual individuals / More promiscuous / More risky and unprotected sexual intercourse / Safer / Other
18) Does your school educate you about sexual health?	Yes / No / Other
19) Do you consider yourself well educated on the topic of safe sex?	Yes / No / Other
20) Do you think there is a need for more guidance and training for your approach to LGBTQIA+ individuals as a physician?	Yes / No / Other
21) Would you refuse to see a patient because they are an LGBTQIA+ individual?	Yes / No / Other
22) Do you think LGBTQIA+ individuals are more prone to catching sexually transmitted diseases?	Yes / No / Other
23) Do you think you would approach patients differently if they lived a life you do not agree with?	Yes / No
24) Please explain in a few short sentences how you would approach an LGBTQIA+ patient.	

The participants were asked whether it was deemed appropriate to allow LGBTQIA+ individuals to work with children. The answers were 876 (78.5%) "Yes" and 239 (21.4%) "No". There was 1 (0.1%) missing data. Nine hundred and ninety-two (88.9%) of the participants thought that LGBTQIA+ were being abused in our society, while 123 (11.0%) of the participants thought that this was not the case according to the 12th question. There was 1 (0.1%) missing data. In addition, while 874 (78.3%) people believed that LGBTQIA+ individuals should be fully accepted in our society, the rest of them (240, 21.5%) insisted that they should not be accepted. There were 2 (0.2%) missing data.

Question 14 was asking if LGBTQIA+ individuals have the right to marry. In the 15th question, it was asked whether LGBTQIA+ individuals should have the right for adoption. The answers that are given to question 14 and 15 are listed in Table 4.

Seven hundred forty (66.3%) participants thought that same-sex marriage does not endanger the concept/ideology of a family, 341 (30.6%) of them defended it does, 19 (1.7%) of them thought it somewhat does, 8 (0.7%) of them were indecisive, 4 (0.4%) of them did not have a particular idea, and there 4 (0.4%) missing data.

The participants were asked how are the sexual behaviors of LGBTIA+ individuals according to their thoughts (Table 5). The participants could choose more than one choice according to their ideas.

It was asked if the participants had education about sexual health in their schools. Similarly, in the 19th question, the participants were asked whether they find themselves as educated about safe sexual intercourse as an individual or not. In the survey, it was asked whether they needed more guidance and training concerning their approach towards LGBTQIA+ individuals as a physician. The answers given to the questions are summarized in Table 6.

One thousand ninety-nine (98.5%) of the participants declared that they would examine an LGBTQIA+ patient, while 13 (1.2%) of them indicated that they would refuse to examine. There were 4 (0.4%) missing data.

Six hundred and eighty (60.9%) participants considered LGBTQIA+ individuals more prone to catching sexually transmitted diseases, while 375 (33.6%) of the participants did not. Twenty-seven (2.4%) participants chose the answer "sometimes," and 23 (2.1%) did not have a particular idea. There were 11 (1.0%) missing data.

Participants were also asked if they would treat their patients differently who had a lifestyle that they did not approve of. Seventy-six (6.8%) of them said "yes," 996 (89.2%) of them said "no," 40 (3.6%) of them said "sometimes," and 3 (0.3%) of them did not have a particular idea. There was 1 (0.1%) missing data. The results of the comparison between the 1st and 6th-grade students are shown in Table 7, 8, and 9.

There is a statistically significant difference between the answers given by 1st and 6th grade students to the 15th question asking whether LGBTQIA+ individuals have the right to adoption or not, to the 18th question asking if their school is providing education on sexual health, to the 19th question asking if they consider themselves educated about safe sexual intercourse as an individual and to the 22nd question asking if they think that LGBTQIA+ individuals are more prone to catching sexually transmitted diseases (p<0.005).

Table 2: Medical school grades' distribution of the participants.

Grades	Number of students (n)	Percentage (%)
1	263	23.6
2	315	28.2
3	179	16.0
4	112	10.0
5	98	8.8
6	139	12.5
Missing	10	0.9
Total	1116	100.0

Table 3: Sexual orientations of the medical students.

Sexual orientation	Number of students (n)	Percentage (%)
Heterosexual	971	87.0
Bisexual	54	4.8
Homosexual	38	3.4
I do not prefer to specify	37	3.3
Other	7	0.6
Pansexual	4	0.4
Asexual	3	0.3
Heteroflexible	1	0.1
Missing	1	0.1
Total	1116	100.0

Table 4: Numeric data of the answers of questions 14 and 15.

Answers	Question 14		Question 15	
	Number of students (n)	Percentage (%)	Number of students (n)	Percentage (%)
Yes	887	79.5	758	67.9
No	184	16.5	276	24.7
Other	29	2.6	45	4.0
No idea	9	0.8	32	2.9
Missing	7	0.6	5	0.5
Total	1116	100.0	1116	100.0

Table 5: Sexual behaviors of LGBTQIA+ individuals.

Answers	Number of students (n)	Percentage (%)
Same with heterosexual	572	40.5
Riskier	383	27.1
More complicated	288	20.4
Safer	49	3.5
No idea	29	2.1
Cannot be generalized	15	1.0
Unhealthy	5	0.4
Other	64	4.5
Missing	10	0.7
Total	1415	100.0

Table 6: Numeric data of the answers of questions 18, 19 and 20.

Answers	Question 18		Question 19		Question 20	
	Number of students (n)	Percentage (%)	Number of students (n)	Percentage (%)	Number of students (n)	Percentage (%)
Yes	495	44.4	883	79.1	857	76.8
No	552	49.5	196	17.6	240	21.5
Partially	43	3.9	30	2.7	14	1.3
No idea	15	1.3	3	0.3	0	0.0
Missing	11	1.0	4	0.4	5	0.5
Total	1116	100.0	1116	100.0	1116	100.0

Table 7: Comparison of the 1ˢᵗ and 6ᵗʰ graders' answers by percentage.

Grades	1ˢᵗ grade		6ᵗʰ grade		P value
Questions/Answers	Yes	No	Yes	No	
Do you consider yourself a religious person?	35.6%	64.4%	36.2%	63.8%	0.905
Is there someone who is LGBTQIA+ among your friends, relatives or people around you?	61.7%	38.3%	52.2%	47.8%	0.067
Would you accept an LGBTQIA+ individual as your friend?	91.6%	8.4%	84.8%	15.2%	0.038
Do you think LGBTQIA+ people have psychological disorders and need therapy?	21.1%	78.9%	26.8%	73.2%	0.195
Do you think that accepting LGBTQIA+ individuals as "normal" will benefit our society?	81.6%	18.4%	72.5%	27.5%	0.035
Do you find it appropriate to allow LGBTQIA+ individuals to work with children?	83.1%	16.9%	71.7%	28.3%	0.008
Do you think LGBTQIA+ individuals are mistreated in your society?	90.4%	9.6%	84.8%	15.2%	0.093
Do you think LGBTQIA+ individuals should be fully accepted in our society?	79.6%	20.4%	72.5%	27.5%	0.106
Would you refuse to see a patient because they are an LGBTQIA+ individual?	0.8%	99.2%	1.4%	98.6%	0.611

Table 8: Comparison of 1st and 6th graders' answers to gender by number and percentage.

Grade	1ˢᵗ grade			6ᵗʰ grade			P value
Gender/ statistics	Number	% within the class	% within the comparison	Number	% within the class	% within the comparison	
Homosexual	12	4.6%	70.6%	5	3.6%	29.4%	0.327
Heterosexual	219	83.9%	64.0%	123	89.1%	36.0%	0.327
Bisexual	16	6.1%	80.0%	4	2.9%	20.0%	0.327
Asexual	1	0.4%	100.0%	0	0.0%	0.0%	0.327
I do not prefer to specify	9	3.4%	60.0%	6	4.3%	40.0%	0.327
Pansexual	1	0.4%	100.0%	0	0.0%	0.0%	0.327
Other	3	1.1%	100.0%	0	0.0%	0.0%	0.327

Table 9: Comparison of 1st and 6th graders' answers by percentage.

Grades	1st grade				6th grade				P value
Questions/ Answers	Yes	No	No idea	Other	Yes	No	No idea	Other	
Do you think LGBTQIA+ individuals have the right to get married?	83.8%	13.5%	1.2%	1.5%	71.7%	25.4%	0.7%	2.2%	0.029
Do you think LGBTQIA+ individuals should have the right to adopt?	71.6%	19.9%	3.4%	5.0%	61.6%	35.5%	0.0%	2.9%	0.001
	Yes	No	Hesitant	Other	Yes	No	Hesitant	Other	
Does same-sex marriage endanger the ideology of a family?	30.3%	66.3%	1.9%	1.5%	35.8%	62.8%	0.7%	0.7%	0.590
	Yes	No	Partially	Other	Yes	No	Partially	Other	
Does your school educate you about sexual health?	36.0%	53.3%	5.4%	5.4%	49.3%	49.3%	1.4%	0.0%	0.003
Do you consider yourself well educated on the topic of safe sex?	67.8%	28.4%	3.1%	0.8%	92.8%	5.8%	1.4%	0.0%	0.000
Do you think there is a need for more guidance and training for your approach to LGBTQIA+ individuals as a physician?	76.9%	21.2%	1.9%	0.0%	71.0%	29.0%	0.0%	0.0%	0.067
Do you think LGBTQIA+ individuals are more prone to catching sexually transmitted diseases?	48.6%	46.3%	2.3%	2.7%	81.2%	16.7%	1.4%	0.7%	0.000
Do you think you would approach patients differently if they lived a life you do not agree with?	6.1%	90.4%	3.4%	0.0%	4.3%	92.8%	2.9%	0.0%	0.809

DISCUSSION

Although it has been 47 years since the removal of homosexuality as a "behavioral disorder" subdivision from DSM, the perspective of professionals towards LGBTQIA+ patients remains an important issue (13, 14). For example, according to a study conducted by Yılmaz et al. (15), nearly 8% of LGBT individuals cancel or postpone physicians' visits with the fear of being discriminated against or judged (15). Therefore, our study, which was conducted on Turkish, German, and Bosnian medical schools aimed to evaluate the attitude of medical students towards the LGBTQIA+ community.

A similar study conducted at Ege University School of Medicine's fourth and fifth-grade students by Ertuğrul et al. (16) aimed to assess the medical students' attitude towards LGBTQIA+ patients. Their questionnaire also consisted of questions regarding the participants' gender, sexual orientation, and possible approaches to LGBTQIA+ patients. In their study, 83.5% of the participants identified themselves as heterosexual while the rest of the students were distributed as 7.8% bisexual, 2.9% asexual, 1.9% gay, and 1% lesbian which is very similar to our results (16). The general distribution of sexual orientation was also similar in a study conducted by Liang et al. (17) at Boston University School of Medicine. This could indicate that the distribution of sexual orientation does not differ drastically from country to country. Based on their findings, Ertuğrul et al. (16) also stated that 52.4% of the participants could be influenced by their beliefs, feelings, or thoughts while interviewing a patient. In our study, participants were asked if they would have treated a patient differently with a lifestyle outside of their approval, and 89.2% said "No." In comparison with their study, they included the participants' high schools, their learning resources regarding the concept of LGBTQIA+, and three patient scenarios to question students' approaches in the questionnaire. Our study aimed to acquire a general opinion of medical students from all grades and different schools, whereas Ertuğrul et al. (16) mainly focused on determining the approach of the future doctor (4th and 5th-year medical students) towards LGBTQIA+ individuals by asking more scenario-based questions.

Another study conducted on Hong Kong Chinese medical students by Hon et al. (18) evaluates the medical students' attitudes and personal experiences regarding homosexuality. In their cross-sectional study, 38% of the students stated that they had homosexual friends (18). Comparatively, the percentage of students who have an LGBTQIA+ friend/relative was higher (57.3%) in our study. This variation could be a result of the wider defi-nition of the focus group in our study. Eighty-six percent of their participants said that they would accept a homosexual individual as their friend, and our studies' findings were also similar (18). As their data implied, 25% of the students had thought that homosexuals have psychological disorders and need therapy (18). In our study, the same question was asked for LGBTQIA+ individuals, and the result was similar. The study conducted by Hon et al. (18) was specific for homosexuality, whereas our study had a wider scope on the subject.

In our study, 76.8% of the participants agreed that there should be more guidelines and training regarding physicians' approaches towards LGBTQIA+ patients. In a survey study conducted on Canadian medical students, 84.5% of the students have also expressed the necessity of further education regarding the issues of the LGBTQIA+ community (19).

Our study also included an open-ended question, asking the participants to explain in a few sentences how they would approach an LGBTQIA+ patient. Many participants have responded that they would treat them the same way they treated other patients. Some participants have also added that they would be more mindful of infections and/or diseases that have a higher prevalence in the LGBTQIA+ community. Some participants expressed that they would refuse to examine the patient. One notable answer stated that the participant would avoid physical contact if the LGBTQIA+ patient is the same gender as he/she is. This negative behavior of some participants towards LGBTQIA+ individuals may indicate either homophobic notions or lack of knowledge about LGBTQIA+ community. The open-ended questions also showed the awareness of many medical students about the necessity of making LGBTQIA+ individuals more comfortable. "As a physician, I will either have a rainbow flag in my room or a rainbow pin on my uniform. Because the smallest support can have a lifelong impact on our relationship with the patients." was noted as one of the remarkable answers. Besides, one of the answers from a Turkish participant expressed his concern regarding the medical computer systems allowing only two genders as possible entries. This is only one of many indications that systematic changes are required in medical systems and communities to provide more inclusion and representation.

The comparison of the answers given by 1st and 6th-grade students disclose a clear difference between the attitude of these two groups of medical students. One of the most noticeable differences was that while 16% of 1st-grade students stated to be LGBTQIA+, this proportion was 11% amongst the 6th-grade students. Collateral to this, 1st-grade students have more LGBTQIA

people as their friends or relatives. Around 36% of the students in both groups stated that they consider themselves religious, however, when examined, their outlook on LGBTQIA+ individuals was quite different. This may be further indication that religion may not have a direct effect on the way certain participants would approach LGBTQIA+ individuals. For instance, 26.8% of 6th-grade students still consider LGBTQIA+ people as psychologically ill, while this proportion is lower by 5.7% among 1st-grade students. Similar differences can be seen on further questions in the survey, revealing the higher tendency of intolerance amongst 6th-grade students. The results in a study conducted by White et al. (20) are similar to ours when it comes to lower grade students, 86.0% of the 2nd-year students stated they would feel more comfortable examining an LGBT patient compared to 82.1% of 3rd and higher-grade students. One more noteworthy study by Nama et al. (19) found more accepting and positive answers from younger individuals regarding the LGBTQIA+ community. This gap could be attributed to the absence of LGBTQIA+ related didactic material in the medical curriculum or the incline of the younger students to be more open-minded to different lifestyles.

Another comparison can be made according to the statistically significant difference found among the groups when asked if the participant thinks LGBTQIA+ individuals are more prone to sexually transmitted diseases. Eighty-one percent of 6th-grade students answered "yes," as the percentage of this answer was 48.6% among the 1st-grade students. Some students emphasized the fact that practicing same-sex intercourse, especially in the male population, without proper protection is a risk factor for certain sexually transmitted diseases.

On the other hand, taking into account the lack of knowledge 1st-grade students have about sexually transmitted diseases compared to the 6th-grade students, there is a possibility they may have overlooked this aspect while answering the question. This comparison does not necessarily mean that 6th-grade students are more biased towards the LGBTQIA+ patients, which is still a possibility that they may have answered the question from a different point of view.

There was also a statistically significant difference found among the 1st and 6th-grade students' answers to whether they consider themselves educated about safe sexual intercourse. This could be associated with many factors such as age, individual experiences, and knowledge. Moreover, there was also a statistically significant difference found among the groups whether their school provided them with education on sexual health. However, this is not enough to explain the aforementioned

differences, since the participants in our study are from various schools and countries with different curriculums which may or may not include safe sexual practices.

Bearing in mind that 6th-grade students are going to be enrolled in the medical field as physicians in the following year, the higher prevalence of the negative perspective spotted may be a major issue for LGBTQIA+ patients in the future. A review published by Gates et al. (21) points out that around 4% of the American population is openly LGBTQIA+ individuals. Assuming this, the rate would not drastically vary between countries meaning that every physician will supposedly encounter hundreds of LGBTQIA+ patients throughout their professional careers. Even though nearly 90% of the participants stated they would not treat their LGBTQIA+ patients any different, several studies demonstrate that LGBTQIA+ patients feel uncomfortable being treated by a physician who lacks sensitivity or information about their sexual orientation (22, 23). All of these factors endanger the proper utilization of healthcare services LGBTQIA+ individuals will receive. The importance of proper education about the LGBTQIA+ people should once again be taken into consideration.

Several studies have shown that it is not only possible to have a positive outcome by incorporating diversity in educational programs towards raising awareness, but also how fast this outcome could be (24). As a great model, Kelley et al. (24) demonstrated how it is possible to positively change perspective, raise awareness and increase the number of people willing to treat LGBTQIA+ patients among medical students' by implementing LGBT health in their curriculum in University of California.

Our study has several limitations. First of all, the participants of the study were not randomly selected, they voluntarily took part in the survey. This might have had a more positive impact on our results owing to students who are already more accepting and informed about LGBTQIA+ individuals to gravitate towards filling out our survey. Furthermore, the participants were not evenly distributed among grades. The difference in numbers might have affected the distribution of the answers. Despite the data privacy and informed consent statement at the beginning of the survey, participants might have had concerns regarding the data security of the survey. This might have influenced the accuracy of some answers given, especially to questions on more sensitive topics, such as the sexual orientation of the participant. Furthermore, some questions in the survey were limited to only allowing "yes" and "no" as answers. This not only ignores the possible answers in-between, but also forces the students, who have not had thought about the certain topic of the question, to pick one answer. Some partici-

pants have also expressed their opinions about how certain questions were phrased. For example, in the case of question 10 which is phrased as: "Do you think it would be beneficial to the society to recognize LGBTQIA+ individuals as 'normal'?", a participant has stated that this question could be answered in two different ways. The participant's answers were "Yes-normalizing the perception would cause an individual to behave differently in a negative manner. No- categorizing the LGBT community as normal would contradict with the concepts of freedom and diversity."

In conclusion, though the majority of answers given indicate a positive approach towards LGBTQIA+ individuals, it can be stated that the attitude of medical students towards LGBTQIA+ individuals is by far suboptimal, especially taking the positively leaning nature of the conducted study into consideration. For instance, a quarter of participants still consider homosexuality as a psychological disorder. Despite this, most of the participating students stated that they would accept LGBTQIA+ individuals as their patients. Yet it is open to discussion on how comfortable these individuals would feel being examined by medical professionals not approving their sexual orientation. It should also be stated that medical students with a positive perspective towards LGBTQIA+ individuals seem to be more aware of the importance of how much their comfort would benefit the healthy relationship between the physician and the patient. Another important result of the study has shown that the vast majority of the students do not think that they are properly being educated about the correct way to approach LGBTQIA+ individuals. Proper education about the sexual health issues and gender minorities in the medical curriculum could play a crucial role in raising social awareness and overcoming prejudices among medical students. Further studies are needed to thoroughly understand the medical students' perspectives on LGBTQIA+ community and patients.

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EVALUATION OF PHYSICAL EXERCISE'S EFFECTS ON LOW BACK PAIN AMONG UNIVERSITY STUDENTS WITH SHORT FORM-36 AND OSWESTRY DISABILITY INDEX

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ABSTRACT

Aims: This study aims to investigate the main effects of physical exercise on lower back pain with the Short Form-36 Health Survey and Oswestry Disability Index scores. ***Methods:*** University students between 18-25 years old who suffer from low back pain were enrolled in the study. Short Form-36 Health Survey and Oswestry Disability Index were used as the reference scales of lower back pain and quality of life, respectively. There are some questions in the questionnaire to scale the average comfort of the place they sleep and sit during the day, which is the result of the Personal Comfort Score. The Mann-Whitney U test was used for non-normal distributed variables. Correlation and Linear Regression were used to analyze data. SPSS 25.0 was used for all statistical analysis. ***Results:*** A total of 139 university students (94 females, 45 males) were included in the study. The median age was 20 years (IQR=2) for female students and 20 years (IQR=1) for male students. Oswestry Disability Index scores of female students were higher, while Short Form-36 scores were lower than the male students. Male students' physical functioning scores were higher than female students. Each one-unit increase in Personal Comfort Score is associated with an increase in the rate between the energy/fatigue (3.34 units). Body Mass Index considerably affected the pain and Oswestry Disability Score, an increase in one unit of baseline BMI upsurged the Short Form-36 pain score to 0.13, and Oswestry disability score to 0.55. ***Conclusion:*** In our study, Body Mass Index is found to be associated with Oswestry Disability Index and Short Form-36 score, which are used for the severity of low back pain and defining the life quality and of patients. PCS had a positive correlation between energy/fatigue. In addition, There was a positive correlation between physical exercise and general health score. ***Keywords:*** Low back pain, physical exercise, Body Mass Index, Short Form-36, Oswestry Disability Index

INTRODUCTION

Low back pain (LBP) is a condition caused by the strain of the muscles or the ligaments in the spine or caused by the compression of the nerve roots (1). It is one of the most significant primary global health conditions as it is the most common reason for limitation and loss of labor (2, 3). It is reported that 70-80% of the people living in Turkey suffer from LBP at least once in their lives (4). LBP is a common health problem among

university students with different percentages. LBP prevalence is reported 65% among the Malaysian medical students and 38% among the dental students (5, 6).

Lower back pain has an enormous impact on our activities of daily living (ADL) such as walking, bending, bathing, getting dressed, or cooking. An Austrian study, including elderly patients, found an apparent association between LBP and problems in ADL (7). LBP also has an effect on the governments' economic burden on healthcare systems (8). According to Diele-

man et al. (9), money spent on LBP and low-neck pain (LNP) has increased over the last 18 years by almost $57.2 billion in the United States. In 2013, $87.6 billion was spent on healthcare for LBP and LNP and made it the third-most costly health problem in 2013 (9).

Although plenty of research has been made on LBP, the leading cause of the disease remains unknown. There are many different factors thought to play a role in LBP, including body mass index (BMI), psychiatric disorders, mobility, gender, and age (10). The majority of LBP is categorized as non-specific LBP. Therefore, further research should be done to better understand the cause in order to enhance the prognostic plans used (11). Hence, analyzing the causes and results of this health condition is crucial to optimize preventive strategies, improve the overall economy, and better the quality of life. In addition, there is a lack of research done to determine the effects of routine physical exercises on LBP (12, 13).

Many different scales have been formed to define people's life quality and physical functioning. The two commonly used ones are Short Form-36 (SF-36) and the Oswestry Disability Index (ODI) (14). The ODI is reported acceptable for measuring disabilities related to LBP by the International Forum for Primary Care Research on LBP while the SF-36 questionnaire is a health-related quality of life measurement that has been extensively used in observational studies for various conditions (15).

This study aims to investigate the effects of physical exercise on the SF-36 and ODI scores on university students at the age of 18-25 experiencing LBP. For this purpose, differences between physical functioning and gender; energy and Personal Comfort Score (PCS); pain and gender; general health and weekly exercise time; pain and BMI; ODI score and BMI were compared among the university students with the age of 18-25 from three different universities in Turkey.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethical Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK2019/471). Participants' informed consents were taken online in written format before filling the questionnaire. Data were collected from the students from Trakya University, Bahçeşehir University and Yeditepe University from October 2019 to January 2020. The online questionnaire form was distributed to universities. The main group of the study was 18-25 years old university students who suffer from LBP. One hundred forty-four participants completed the whole online questionnaires, which include age, sex, alcohol/smoking/drugs addiction, university, year at the university, number of steps per day, hours of sleep per night, PCS which is attained by the questions about the comfort of the accommodation and sleep, hours of physical exercise per week, comorbidities, LBP levels, SF-36 and ODI tests, weight, and height (BMI). Exclusion criteria include factors such as the age of students, stage of the disease, the subject's previous treatment history, and the presence of any psychosocial and emotional conditions. Therefore, five students were excluded from the present study, related to the orthopaedical disabilities (arthritis, fractures, scoliosis) and the questionnaires with invalid responses. In the end, a total of 139 university students (94 females, 45 males) were included in the study.

Turkish versions of SF-36 and ODI were used as the reference scales for quality of life and pain. Validations of these scales were researched in advance (16, 17). ODI is a test composed of 10 questions and it is scored between 0-5. In order to find the ODI score, the values of the participants' answers are summed then doubled. Score zero corresponds to no disability, while score 5 corresponds to maximum possible disability (18). SF-36 is a test with 36 questions scored between 0 - 100. Every subheading is scored by the average of relevant questions from the test. ODI was evaluated with one final score, and SF-36 was evaluated with eight different scores being: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. PCS is the average comfort of the places where they sleep and sit during the day. Scaling of PCS is between 0 - 10, which selecting 0 means least comfortable, and selecting 10 means the most comfortable place. Weekly exercise time as the hour was used to evaluate the physical exercise (16, 17).

Statistical Package for the Social Sciences (SPSS) version 25 was used to analyze the data. The Kolmogorov-Smirnov test was used as a test of normality. Descriptive statistics of continuous variables (age, BMI, PCS, weekly physical exercise time, numbers of step per day, physical functioning, physical role functioning score, emotional role functioning score, energy/fatigue score, emotional well-being score, social functioning score, pain score, general health score and ODI score) were given as median and IQR. Since all of the aforementioned variables were distrubted non-normally, Mann-Whitney U test was used to compare the data. Categorical data (gender, universities and participants' grades) were presented as numbers

(n) and percentages (%). Correlation between BMI, numbers of step per day, ODI Score, SF-36 subheadings, PCS and weekly exercise time were analyzed.

Differences between ODI score and gender and SF-36 subheadings' scores and gender were analyzed by Mann-Whitney U test. ODI score and age; SF-36 subheadings' scores and age; ODI score and PCS; SF-36 subheadings' scores and PCS; ODI score and weekly exercise time; SF-36 subheadings' scores and weekly exercise time; ODI score and BMI: SF-36 subheadings' scores and BMI; ODI score and average daily steps; SF-36 subheadings' scores and average daily steps; ODI score and daily studying time; SF-36 subheadings' scores and daily studying time were analyzed by univariate linear regression tests. (ODI score and SF36 subheadings' scores are dependent variables whereas age, PCS, weekly exercise time, BMI, average daily steps, and daily studying time are independent variables. The residuals of the regression follow normal distribution.) For all statistical comparisons, p<0.05 was assumed to indicate statistical significance.

RESULTS

In total, the responses of 139 students were included in this study. There were 94 (67.63%) female students, and 45 (32.37%) male students. Their median age was 20 years. Descriptive statistics of the participants are shown in Table 1. Most of the students were from Trakya University (60.43%), and the least was from Bahçeşehir University (10.8%) (Table 2). Participants were from six different grades, and the number of participants was decreasing in every grade (Table 3).

The median age of participants was 20 years for females and 20 years for males. The age difference between gender groups was not statistically significant (p=0.854). Median BMI's of participants was calculated as 20.45 for females and 24.45 for males. Differences between groups were statistically significant (p<0.001). Median PCS's were calculated as 6.66 for females and 7 for males. Differences between groups were not statistically significant (p=0.453). Medians of weekly exercise time in hours were calculated as 2.5 for the female group and 5 for the male group. Differences in median levels of groups were statistically significant (p<0.001). The median of daily steps was 7000 for the female group and 8000 for the male group. Differences between groups were not statistically significant (p=0.109). Median levels of physical role functioning, emotional role functioning, energy /fatigue, emotional well-being, social functioning and general health between two genders weren't statistically significant (p=0.824, p=0.981, p=0.11, p=0.338, p=0.177, p=0.13, respectively). Differences in median levels of physical functioning, pain, and ODI sco-

Table 1: Universities of participants.

	Numbers (n) / Percentage (%)
Trakya University	84 (60.43%)
Yeditepe University	40 (28.77%)
Bahçeşehir University	15 (10.8%)

Table 2: University grades of the participants.

	Numbers (n) / Percentage (%)
1st Grade	48 (34.53%)
2nd Grade	43 (30.94)
3rd Grade	17 (12.23%)
4th Grade	18 (12.95%)
5th Grade	9 (6.47%)
6th Grade	4 (2.88%)

Table 3: Comparison of parameters by gender.

	Female [median (IQR)]	Male [median (IQR)]	p-value	Total Median (IQR)
Age (years)	20 (2)	20 (1)	*0.854*	20 (1)
BMI* (kg/m²)	20.45 (3.73)	24.45 (4.6)	*<0.001*	21.09 (5.66)
PCS	6.66 (1.33)	7 (1)	*0.453*	6.67 (1.33)
Physical Exercise (h/week)	2.5 (3)	5 (5)	*<0.001*	3 (4)
Number of Steps per Day	7000 (4000)	8000 (4000)	*0.109*	7000 (3000)
Physical Functioning	90 (16.25)	100 (10)	*<0.001*	95 (15)
Role Functioning / Physical	75 (75)	75 (75)	*0.824*	75 (75)
Role Functioning / Emotional	33.33 (33.33)	33.33 (83.33)	*0.981*	33.3 (66.6)
Energy / Fatigue	50 (30)	50 (25)	*0.11*	50 (30)
Emotional Well-Being	56 (32)	60 (22)	*0.338*	56 (24)
Social Functioning	62.5 (32.5)	87.5 (32.5)	*0.177*	75 (37.5)
Pain	77.5 (27.5)	90 (32.5)	*0.001*	77.5 (27.5)
General Health	60 (30)	65 (25)	*0.13*	60 (25)
ODI (%)	12 (16)	8 (17)	*0.028*	12 (17.5)
Gender [number (%)]				Male = 45 (32.37%) Female = 94 (67.63%)

BMI: *Body Mass Index,* **PCS:** *Personal Comfort Score,* **ODI:** *Oswestry Disability Index. Independent samples test * Mann Whitney U Test*

res between two genders were statistically significant (p<0.001, p=0.001, p=0.028, respectively) (Table 4).

The results of our study revealed that the collected data from female participants had a negative correlation between physical functioning and pain scores for SF-36 (r=-0.4325) (p=0.839). Male participants' physical functioning scores were 5.98 units higher than females', and also their pain scores were 10.58 unit higher than females' (p=0.024, p=0.002, respectively). Every 1 unit increase in PCS is associated with 3.34 units increase in the rate between the energy/fatigue (r=0.1844, p=0.03). Each hour of physical exer-

cise increases the general health score with 1.10 units (r=0.2067, p=0.015). Our results showed that BMI considerably affects the pain and ODI score numerically positive. With every increment in BMI baseline, SF-36 pain score increases by 0.13 and ODI score by 0.55 (r=0.1033, p=0.048; r=0.1113, p=0.04, respectively).

There was no significant difference found in ODI and age; SF-36 subheadings' scores and age; ODI and PCS; ODI and weekly exercise time; ODI and number of steps per day; SF-36 subheadings' scores and number of steps per day; ODI and daily studying time; SF-36 subheadings' scores and daily studying time between genders.

DISCUSSION

Lower back pain is a general and serious discomfort between university students. The present study showed that BMI was a factor affecting ODI and SF-36 scores, which are used to define life quality and LBP seriousness. This study revealed that the comfort of places we sit and sleep during the day, PCS, had a positive correlation with energy/fatigue. This finding may indicate that when PCS is increased, energy increases whereas fatigue decreases, as expected. In addition, there was a positive correlation between physical exercise and general health score. Since gender is a non-modifiable risk factor for LBP, improving modifiable factors such as exercise and PCS may play a major role in increasing the quality of life and decreasing LBP.

In this study, life quality and LBP were evaluated thorough ODI and SF-36. It is found that ODI and SF-36 are affected by BMI. SF-36 contains eight domain scores, including "physical functioning" (19-21). This domain asks respondents about limitations on their mobility activities. Musculoskeletal pain (MSP), which also includes LBP is a health problem seen in the adolescent population at a rate of 4-40% (22). In the study of Guite et al. (23), it has been shown that MSP affects overall life quality by causing physical disability. In their study, the mean age (15 ± 1.4 years) was lower than our study. They used The Functional Disability Inventory instead of ODI and The Self-Perception Profile for Adolescents instead of SF-36 (23). In spite of having the similar result about muscle pain's effects, the aims of these two studies had a major difference; our study was aiming to reveal the factors that may be related to LBP, whilst the prementioned study was aiming to reveal the results of MSP. Our study revealed a positive correlation between the life quality and physical exercise in one subheading of SF-36, general health. In the other seven subheadings, our study demonstrated that the correlation between life quality and physical exercise was not statistically significant.

Our study showed that the comfort of places we sit and sleep during the day, PCS, affects our overall energy and fatigue during the day. Some studies stated that fatigue is related to age and gender (24, 25), wheras in our study, there was not any significant difference between genders or age in the ratio of energy/fatigue; it may possibly be due to the age limitation. Our participants were aged between 18 and 25, but the prementioned studies had different limitations, such as 25-74 years. Fatigue is also one of the reasons and symptoms of major depression (25). According to these studies, older people, especially females, had 1.5 times more

possible to experience fatigue (24, 25). Therefore, the discomfort of the places we sit, and sleep may increase the risk of experiencing fatigue. This may play a role in the onset of depression.. In a study done by Corfield et al. (26), out of 10.5% depressed people, 63.8% of them experienced fatigue. In addition, depression is intercorrelated with fatigue. Whilst fatigued people feel more depressed, depressed people feel more fatigue.

Amelot et al. (27) collected information related to a regular exercise routine and type and indicated that regular physical activity decreases LBP occurrence. Although we have only asked weekly exercise time of participants instead of their routine and the type of exercise, we have similar results. Our results showed that there was also a correlation between general health and weekly exercise time. In addition to this finding, Amelot et al. (27) stated that there is a correlation between LBP and gender and LBP has an impact on personal schoolwork, personal life, personal social activities and quality of sleep in 1243 participants. Similarly, the present study revealed a positive correlation between physical functioning and gender in 139 participants.

Muntaner-Mas et al. (28) claimed there was not a significant correlation between the participants in sports and LBP. According to Muntaner-Mas et al. (28), females had more severe LBP than male participants. In our study, SF-36 scores of females were lower than male students, but ODI scores were higher than male participants. Female participants of our study had more severe LBP than males due to the differences in the physical development of participants, daily activities, numbers, and mean age of participants.

Some limitations were recorded in the study. Since the questionnaire was distributed online, the participants did not have a chance to communicate with researchers directly and to overcome misunderstandings. The other limitation was the number of participants. More than 3000 students were contacted, but only 144 have been recorded in the study.

In conclusion, LBP is a common medical problem among university students. Our study showed that there are various factors affecting students' lives positively or negatively according to participants' SF-36 and ODI scores. PCS had a positive correlation between energy/fatigue. In addition, There was a positive correlation between physical exercise and general health score. Students may modify their weekly exercise time and comfort of the places they sit and sleep to increase their own life quality and decrease the problems they face due to LBP. However, further studies are needed in order to elucidate the major causes of LBP.

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KNOWLEDGE LEVEL OF MEDICAL, PHARMACY AND NURSING STUDENTS ABOUT VACCINATION AND VACCINE SAFETY

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ABSTRACT

Aims: This study aims to determine the knowledge level of medical, pharmacy, and nursing students at Trakya University regarding vaccination and vaccine safety. **Methods:** A questionnaire comprised of 8 questions was completed by 383 students in February 2020. Out of 383 participants, there were 143 medical, 95 pharmacy, and 145 nursing students. The relation of knowledge level with gender, faculty, and the grade were evaluated using the Chi-Square test. **Results:** Out of 383 students 19.9% stated that they had no knowledge about national childhood vaccination schedule of Turkey, 14.6% thought vaccines cause autism, 83.7% stated that they do not regularly get vaccines recommended for adults, and 68.6% did not have the proper answer to the question of where vaccination can be applied. **Conclusion:** Vaccines and vaccine safety concerns health care students closely, yet these students have insufficient knowledge about vaccines. As a solution to this problem, more time can be spared for vaccination and vaccine safety subjects in the curriculum of these faculties. **Keywords:** Vaccines, vaccination, autism spectrum disorder, students, questionnaire

INTRODUCTION

There have been numerous claims about vaccines in recent years, putting forth a relation with vaccination and different disorders such as immune system dysfunction, Attention-Deficit/Hyperactivity Disorder (ADHD), and autism. Misleading articles and news published in mainstream media, also support these concerns (1). However, studies are showing that there is no association between autism or ADHD and vaccination (2-5).

Some vaccines contain the microorganism that also causes the disease, but these are attenuated microorganisms and are not harmful to the individual. Other vaccines contain only some parts of the microorganism. Vaccines stimulate the immune system to produce the same antibodies as if the individual faced the disease itself, thus vaccinated individual already has the antibodies, without having the disease (6).

The aim of this study is to determine the knowledge level of medical, pharmacy, and nursing students, who are the future health workers, about vaccination, vaccine safety, and concerns about vaccines.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University Medical Faculty (Protocol Code: TÜTF-BAEK 2019-475). The study was performed on 383 voluntary students in February 2020. Participant group size was specified by taking into consideration the attainability. It is a descriptive, cross-sectional study using a questionnaire consisted of 8 questions. The participants were selected on a voluntary basis and the questionnaires were given to participants by hand. The content of the questionnaire and how the data were going to be used were inscribed at the beginning of the questionnaire. 1st-3rd year medical, 1st-4th year pharmacy, and 1st-4th year nursing students from Trakya University participated in the study. The demographic information consisted of the grade and faculty of the participants were questioned to evaluate the association between demographic data and the knowledge level of participants. The relationship between vaccination preferences, knowledge level, and gender were evaluated accor-

ding to participants' answers to associated questions. The entire questionnaire is presented in Table 1. In the 1st, 3rd, 5th, and 6th questions it was aimed to evaluate the knowledge level of the participants on vaccination, and in the 2nd, 4th, 7th, and 8th questions it was aimed to question participants' general attitude on vaccine and vaccination. The data was analyzed using IBM SPSS version 20.0. Chi-square test was used on categorical variables. In all statistical analyses, a p-value of <0.05 was set for the statistical significance.

Table 1: The questionnaire used in the study.

1- Which one of the below is more descriptive about your knowledge level on national childhood vaccination schedule of Turkey?   *I am knowledgeable and I know each vaccine.*   *I am knowledgeable but I do not know each vaccine.*   *I am uninformed.*
2- Would you consider getting your children vaccinated in the future according to the schedule?   *I consider getting my children vaccinated.*   *I do not consider getting my children vaccinated.*
3- What is your opinion about the idea of vaccination causing autism in children?   *I think vaccination causes autism in children.*   *I think some vaccines cause autism in children.*   *I do not think vaccination causes autism in children.*
4- Do you regularly get vaccinated?   *Yes*   *No*
5- Where do you think vaccination is done?   *Family Medicine Offices*   *Community Health Centre*   *Hospitals*   *Pharmacies*
6- Have you ever heard of the active/inactive vaccine term? Do you have any information?   *Yes, I have heard and I am knowledgeable.*   *Yes, I have heard but I am uninformed.*   *No, I have not heard of it.*
7- Do you find vaccination services in Turkey sufficient?   *Yes, it is sufficient.*   *No, it is insufficient.*
8- Should government follow an obligatory vaccination policy?   *Yes, government should follow an obligatory vaccination policy.*   *No, government should not follow an obligatory vaccination policy.*

RESULTS

Out of 383 participants, 127 (33.2%) were male and 252 (65.8%) were female, 4 (1%) did not specify their genders. Participants who did not specify their genders were included in the study yet excluded from gender-related questions. The demographic distribution of the participants is shown in Table 2.

The first question aims to evaluate the knowledge level of participants about the national childhood vaccination schedule of Turkey. All the faculties were grouped by the grades and compared separately for this question .

Out of 142 medical students; 14 (9.9%) 1st year, 11 (7.7%) 2nd year, and 2 (1.4%) 3rd year students stated that they did not have enough knowledge about the vaccination schedule. 1 participant did not answer the question (Figure 1). Statistically significant association was found between the grade and knowledge level about vaccination schedule among medical students (p=0.049).

Out of 95 pharmacy students; 9 (9.5%) 1st year, 7 (7.4%) 2nd year, 1 (1%) 3rd year, and 3 (3.2%) 4th year students stated that they did not have enough knowledge about the vaccination schedule and statistically significant association was found between grade and knowledge level about vaccination schedule among pharmacy students (p=0.003).

Out of 144 nursing students, 15 (10.4%) 1st year, 10 (6.9%) 2nd year, 3 (2%) 3rd year, and 1 (0.7%) 4th year students stated that they did not have enough knowledge about the vaccination schedule (Figure 2). Statistically significant association was found between the grade and knowledge level about the vaccination schedule among nursing students (p<0.001).

Among participants who stated that they did not have enough knowledge about the national childhood vaccination schedule of Turkey, there were 27 (35.5%) medical, 20 (26.3%) pharmacy, and 29 (38.2%) nursing students. There was no significant difference between the knowledge level of students from different faculties (p>0.05).

The answers to the second question, asking the students if they would vaccinate their child following the national childhood vaccination schedule of Turkey in the future, are grouped by gender. 6 (1.6%) participants stated they would prefer not to; 1 (0.3%) male and 5 (1.3%) female. There was no significant difference between male and female participants for being anti-vaxxer (p>0.05).

In the third question, participants were asked if they think vaccines cause autism and the answers were grouped by the faculty and the grade.

One hundred twenty-five (39%) medical students, 78 (24.4%) pharmacy students, and 117 (36.6%) nursing students had the knowledge that no vaccine had the effect of causing autism in children. There was no significant difference between faculty and knowledge level about vaccines (p>0.05). The distribution of answers to question 3 by participants' grade for each faculty is shown in Table 3. The grade was not found statistically significant for medical students' answers to the third question (p>0.05), yet it was found to be significant for pharmacy (p=0.023) and nursing students (p=0.003).

Out of 383 students, 62 (16.3%) stated that they get their adulthood vaccines regularly while 318 (83.7%) students stated they do not. 3 participants did not answer the question (Figure 3).

Answers of the fifth question, which was asked to determine if students know where vaccination procedures are done, are grouped by the faculties. 87 (33.2%) medical, 73 (27.9%) pharmacy, and 102 (38.9%) nursing students did not have enough knowledge. Statistically significant association was found between knowing where vaccination procedures are done and faculty (p=0.034) (Figure 4).

Knowledge level of participants about active/inactive vaccine was asked in the 6th question and answers were grouped by the grade. The distribution by the grade is shown in Table 4. Statistically significant association between being knowledgeable about active/inactive vaccine and the grade was found for all faculties (p<0.001).

Questions "Do you find vaccination service in Turkey sufficient?" and "Should government follow an obligatory vaccination policy?" were asked to evaluate participants' thoughts and preferences. 186 (49.1%) participants said they find the vaccination service in Turkey sufficient (Figure 5) and 310 (81.2%) think that government should follow an obligatory vaccination policy (Figure 6).

Table 2: The demographic distribution of the participants.

		1st year	2nd year	3rd year	4th year	Total
Faculty	Medicine	46	59	38	-	143 (37.3%)
	Pharmacy	23	33	27	12	95 (24.8%)
	Nursing	38	33	42	31	144* (37.9%)
Gender	Female	62	85	70	35	252 (65.8%)
	Male	42	40	37	8	127 (33.2%)
	Unspecified					4 (1%)

(*1 student from nursing did not specify his class).

Table 3: The distribution of answers by class and faculty on 3rd question.

	Class	Vaccination Causes Autism in Children	Some Vaccines Cause Autism in Children	Vaccination Does not Cause Autism in Children
Medicine (p=0.664)	1st	1 (2.3%)	6 (14%)	36 (83.7%)
	2nd	1 (1.7%)	4 (6.8%)	54 (91.5%)
	3rd	1 (2.6%)	2 (5.3%)	35 (92.1%)
Pharmacy (p=0.023)	1st	1 (4.5%)	7 (31.8%)	14 (63.6%)
	2nd	1 (3%)	1 (3%)	31 (93.9%)
	3rd	1 (3.8%)	4 (15.4%)	21 (80.8%)
	4th	-	-	12 (100%)
Nursing (p=0.003)	1st	-	12 (31.6%)	26 (68.4%)
	2nd	1 (3.2%)	3 (9.7%)	27 (87.1%)
	3rd	1 (2.4%)	7 (16.7%)	34 (81%)
	4th	1 (3.2%)	-	30 (96.8%)

Table 4: The distribution of knowledge level about active/inactive vaccine by class.

	Class	Knowledgeable about active/inactive vaccine	Heard of active/inactive vaccine but is uninformed	Uninformed of active/inactive vaccine
Medicine (p<0.001)	1st	21 (47.7%)	6 (13.6%)	17 (38.6%)
	2nd	29 (49.2%)	20 (33.9%)	10 (16.9%)
	3rd	33 (86.8%)	5 (13.2%)	-
Pharmacy (p<0.001)	1st	7 (30.4%)	6 (26.1%)	10 (43.5%)
	2nd	9 (27.3%)	18 (54.5%)	6 (18.2%)
	3rd	24 (88.9%)	3 (11.1%)	-
	4th	11 (100%)	-	-
Nursing (p<0.001)	1st	10 (27%)	13 (35.1%)	14 (37.8%)
	2nd	18 (54.5%)	9 (27.3%)	6 (18.2%)
	3rd	28 (66.7%)	10 (23.8%)	4 (9.5%)
	4th	30 (96.8%)	1 (3.2%)	-
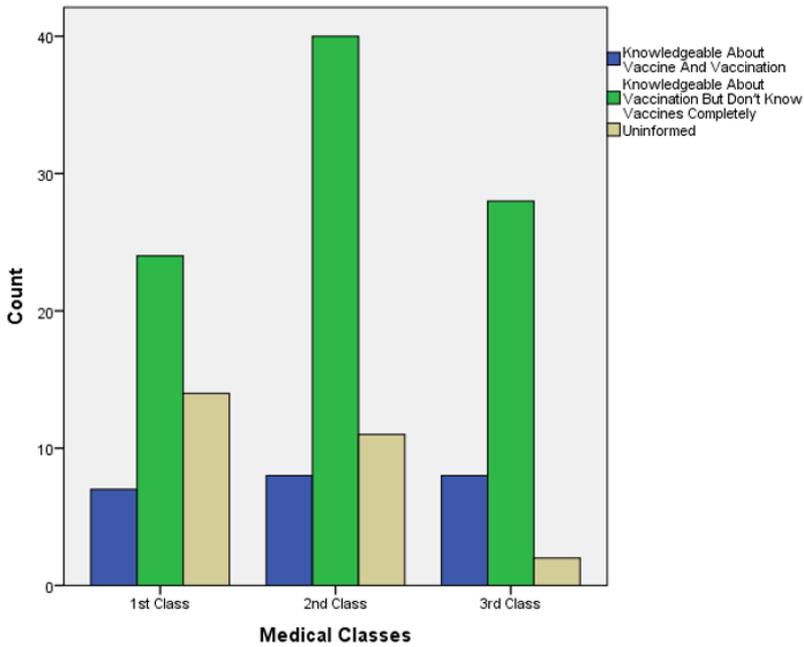
Figure 1: The distribution of medical students' answers by class for the first question.
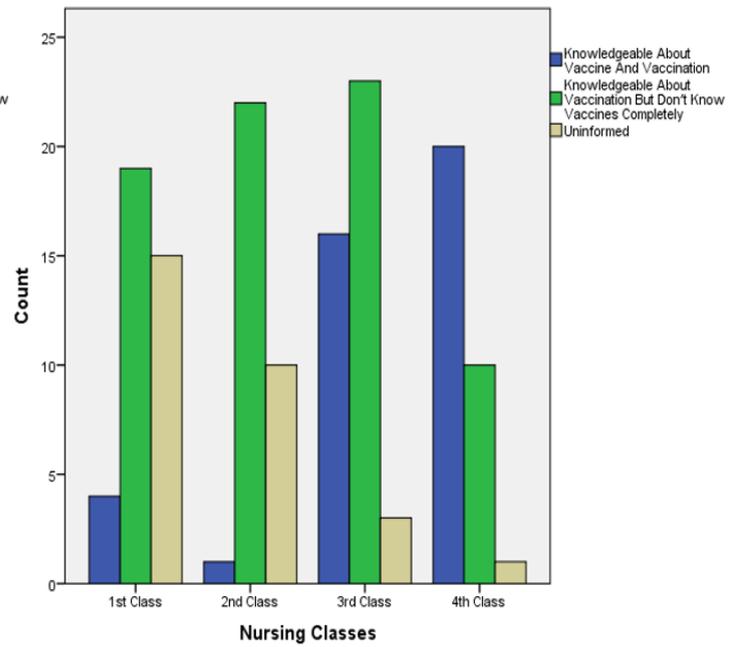
Figure 2: The distribution of nursing students' answers by class for the first question.
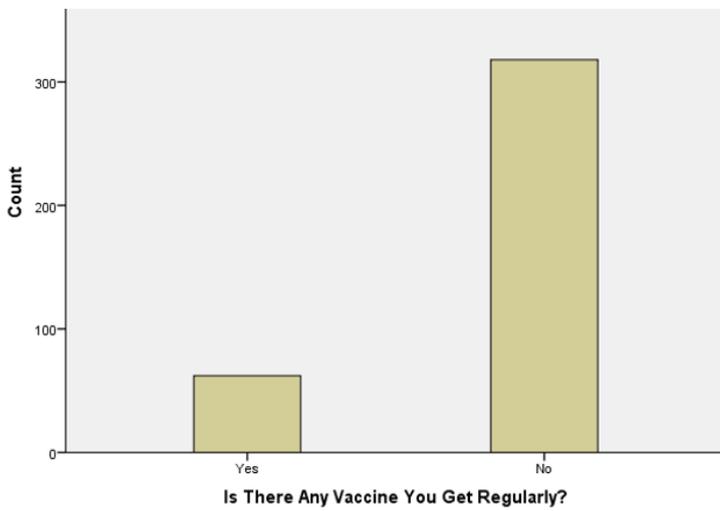
Figure 3: Regularly done adulthood vaccination among participants.
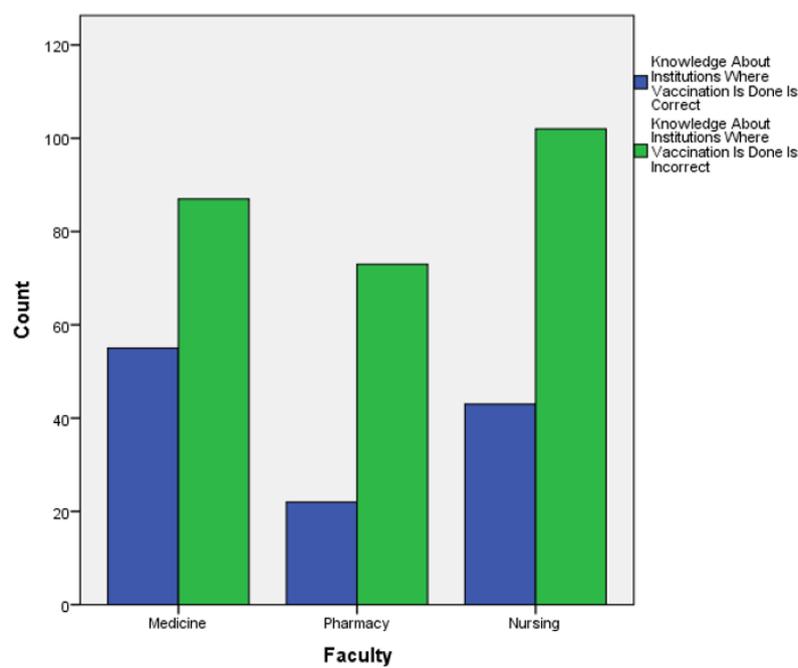
Figure 4: Accuracy of participants knowledge on the question of "Where do you think vaccination is done?".
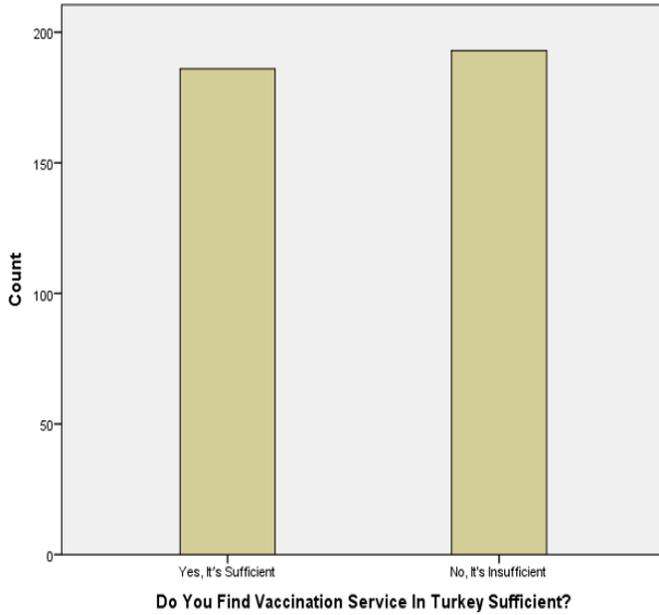
Figure 5: Participants thoughts on vaccination service in Turkey.
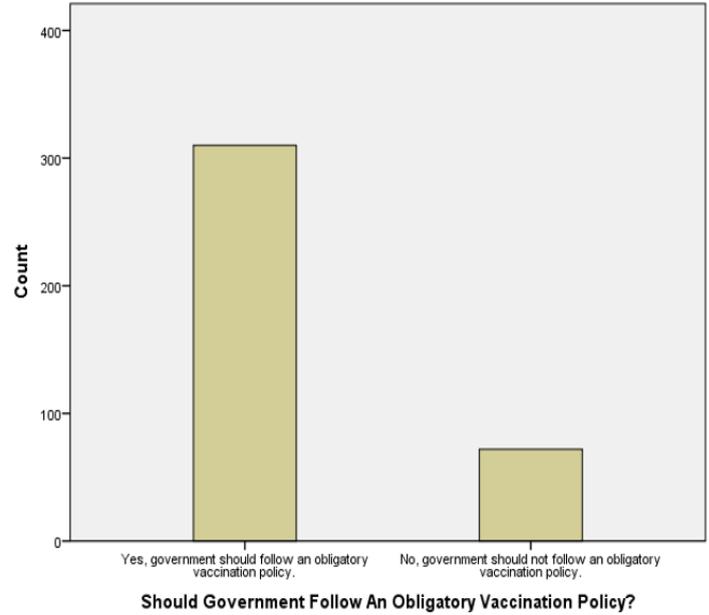
Figure 6: Participants thoughts on obligatory vaccination.

DISCUSSION

There might be differences in vaccination programs for each country. The two most important reasons for that are epidemiology and the presence of an effective, secure, and accessible vaccine (7). Designing vaccination programs and their implementation is carried out by the Ministry of Health, General Directo-

rate of Primary Health Care in the Turkish Republic. Expanded Immunization Program started in 1981 in Turkey (7). The up-to-date national childhood vaccination schedule of Turkey is shown in Table 5 (8).

The results of this study show that students in higher grades' knowledge levels are higher. Feher et al. (9) reported 6.5% of medical students in Hungary had flu vaccination coverage before education, and 24%

Table 5: National childhood vaccination schedule of Turkish Republic.

Age Vaccine	Birth	1 month	2 months	3 months	4 months	6 months	12 months	18 months	24 months	Primary school (1st grade)	Secondary school (8th grade)
Hepatitis B	I	II				III					
BCG			I								
DTaP-IPV-Hib			I	II	III			R			
PCV			I	II			R				
MMR							I			II	
DTap-IPV										R	
OPV						I		II			
Td											R
Hepatitis A								I	II		
Chickenpox							I				

BCG: *Bacillus Calmette-Guérin* **DTaP-IPV-Hib:** *Diphtheria, Tetanus, Pertussis, Polio, Haemophilus influenzae Type b*
PCV: *Pneumococcal conjugate vaccine* **MMR:** *measles, mumps, rubella* **DTap-IPV:** *Diphtheria, Tetanus, Pertussis, Polio*
OPV: *oral polio vaccine* **Td:** *Tetanus, Diphtheria*

of students uninformed about the schedule cannot be ignored. To reduce this number medicine, pharmacy and nursing faculties should focus on the benefits of vaccination in the education curriculum.

Every year, almost 3 million children around the world die of diseases preventable with vaccines (10). The main reason is that efficient immunization for children has a low rate (10). There are three hypotheses of the anti-vaccination movement. The first claim is that Measles, Mumps, Rubella (MMR) vaccine causes the intestinal membrane to break, therefore causing absorption of enzymes causing encephalopathy. The second claim is that ethyl mercury, which is an ingredient of vaccines, is toxic for the central nervous system, and the third claim is that vaccines suppress and weaken the immune system when applied at the same time (11).

In this study, almost all of the students said they would vaccinate their children in the future so it can be said that the anti-vaccination movement is not very common among students in healthcare.

There are still some arguments about studies claiming that vaccination is the cause of autism, ADHD, neurologic diseases, inflammatory bowel diseases, and some immune system dysfunctions. This causes the anti-vaccination movement to grow and some organizations to rise (12). However, there are some strong studies performed against the idea of vaccines causing autism are showing that thimerosal and mercury inside the vaccines or MMR vaccines do not cause autism (13-15). The majority of participants stated they do not believe that vaccines cause autism. Greenberg et al. (16) reported a concerning number of parents who believe or are uncertain about there is a link between vaccines and autism (28%). However, since the population of our study consisted of students who are going to be healthcare providers, the results of our study are different than Greenberg et al. (16).

Many diseases that may cause mortality or morbidity are preventable with vaccination. Tetanus cases reported by the European Union in 2014 consisted of 65% adults. Each adult with unregistered tetanus vaccination information should complete their vaccination by having three doses of adult diphtheria-tetanus vaccine (Td). All adults who have completed their primary vaccine series should get a Td vaccine every 10 years. There are also other vaccines that need to be taken before traveling, pilgrimage, and Umrah visits or because of chronic diseases (17).

Influenza vaccine is recommended for people older than 6 months with risk factors but no contraindication and people older than 65 years with no contraindi-

cation (18). Clinical trials showed influenza vaccines to have a 60% positive impact on people older than 65 (19).

Christini et al. (20) reported 63% of medical students were vaccinated for influenza. Walker et al. (21) reported 53.8% of Australian medical students received most recent influenza vaccine in 2014 and inconvenience was the most common barrier to vaccination among Australian students. In our study, the ratio of getting regularly vaccinated is very low with 16.3% compared to literature. Our results may be caused by personal preferences or lack of education.

Active vaccines are manufactured from a weakened microorganism that causes the disease. Vaccines manufactured this way contain microorganisms and create immune response but do not cause the disease. This type of vaccines should not be used in immunosuppressive patients. Bacillus Calmette-Guêrin (BCG), oral polio, MMR, and chickenpox vaccines are examples of active vaccines. Inactive vaccines such as Hepatitis A, hepatitis B, inactive polio, and pneumococcal vaccines may contain whole microorganisms or only its antigenic units (22).

In this study, 50.9% of students stated that they do not find vaccination services enough, and 81.2% of the students stated that government should follow an obligatory vaccination policy. Accordingly, it can be thought that the students came to this conclusion: If vaccination would not be obligatory, it would not be correctly followed by individuals themselves or anti-vaxxer parents would not vaccinate their children. According to these results and health students' high ratio of awareness about vaccination, in the future, these students might improve vaccination services, search for ideas, create awareness, change behavior, or determine the reason why vaccination services are not enough.

Vaccination in Turkey in recent years has become a controversial issue especially in terms of vaccines applied to children. The issue went ahead of the judiciary, and the Supreme Court ruled that the children could be vaccinated without the consent of their legal representatives. However, upon the decisions of the Constitutional Court that forbid vaccination without consent, the decisions of the Supreme Court changed in this direction. In order to make the administration use vaccination authority, this authority must be based on the law. If the authority is granted by law and also the consent is not stipulated as a condition, the administration does not need the consent of the person concerned about vaccination (23).

This study has some limitations that should be noted. Firstly, our questionnaire was completed by 383

students, further studies with more participants may give different results. Secondly, volunteers of this study consisted of only Trakya University students. Thirdly, only the first three grades of medical students were included in this study although all of the grades of other faculties were included. Fourthly, there are merely 4 questions asked for testing the knowledge level of participants however other questions asked for finding out habits and thoughts of the participants.

In conclusion, healthcare students who have knowledge about vaccines and vaccination can orient both the people around them and their patients correctly in their future professional lives. They can help solve this timely problem by transferring the correct information to the public against vaccine-preventable diseases and anti-vaxxers. In order to make students more informed about vaccines and vaccination, it may be beneficial to include this subject more in the curriculum and to carry out more informative studies on the subject.

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CERVICAL MENINGOCELE IN A NEWBORN: A CASE REPORT

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ABSTRACT

Aims: Neural tube defects are among the most common congenital anomalies worldwide, with a wide range of subtypes. The aim of this case report is to present a patient with cervical meningocele, a rare type of neural tube defect. ***Case Report:*** A 33-year-old pregnant woman with a story of bearing an anencephalic baby was referred to Trakya University Hospital with a probable cystic hygroma diagnosis on the 31st week of pregnancy. An antenatal ultrasound revealed a protrusion on the posterior cervical region. Two days before the planned delivery, fetal magnetic resonance imaging was performed by the decision of the council. The 61 x 37 millimeters cyst was planned to be removed upon birth. On the 38th week, the baby was delivered by cesarean section with no other complications. After a preoperative magnetic resonance imaging, surgical procedure including the excision of the cyst and the duroplasty was performed. ***Conclusion:*** A rare and devastating congenital anomaly, cervical meningocele, requires accurate diagnosis and prompt surgical involvement for effective treatment and good prognosis. ***Keywords:*** Meningocele, cervical meningocele, neurosurgery, neural tube defects

INTRODUCTION

Neural tube defects (NTDs) are congenital anomalies affecting the central nervous system, and originating during embryonic development by incomplete closure of the neural tube (1). NTDs are divided into two groups, spina bifida occulta and spina bifida aperta. Spina bifida occulta can be defined as the neural defect being "closed" by ectoderm, thus preventing cerebrospinal fluid leakage. In a case of spina bifida aperta, however, there is no full coverage by ectoderm. This leaves the neural defect "open", and causes cerebrospinal fluid leakage (2).

NTDs are among the most common congenital anomalies worldwide, occurring at a range of 0.5-10 per 1000 live births, with a geographic variation of incidence (1, 3). The risk for the next pregnancy for couples that had an offspring with an NTD has been reported to be 40 per 1000 live births (4). Meningocele is a type of spina bifida occulta, which appears as a protrusion of the meninges filled with cerebrospinal fluid, often in the lumbosacral region and without being accompa-

nied by neural tissue (5). Thus, neurologic deficits are generally not expected (6). However, the spinal cord may still be tethered, eventually causing symptoms (7). Meningocele cases that affect the cervical region are less frequent, accounting for 1-5% of all NTDs (8). Children with cervical meningoceles should be observed strictly as this particular type of meningocele may be associated with other spinal abnormalities (9). Although the exact cause of this defect is not known, low levels of maternal folate during the early stages of pregnancy, diabetes, and obesity are believed to be involved (1, 10).

CASE REPORT

A pregnant woman was directed to Trakya University Hospital on the 31st week of pregnancy with a suspected cystic hygroma on the baby. After undergoing an antenatal ultrasound, the baby was diagnosed with a cervical meningocele. The mother was 33 years of age, who had a story of labour arrest in her first pregnancy and bearing an anencephalic baby on her second.

She regularly used medication for asthma during this pregnancy. Two days before the planned delivery, she was admitted to the obstetrics service in our hospital. The council decided for an evaluation from the departments of neurosurgery and pediatric surgery, along with fetal MRI. Fetal MRI confirmed that an exophytic cyst of 61 x 37 millimeters covered by a thin layer of skin on the posterior cervical region was present, contiguous with the vertebral column, and contained some septation (Figure 1-3). The right renal pelvis was more prominent than the left. No other abnormalities were detected.
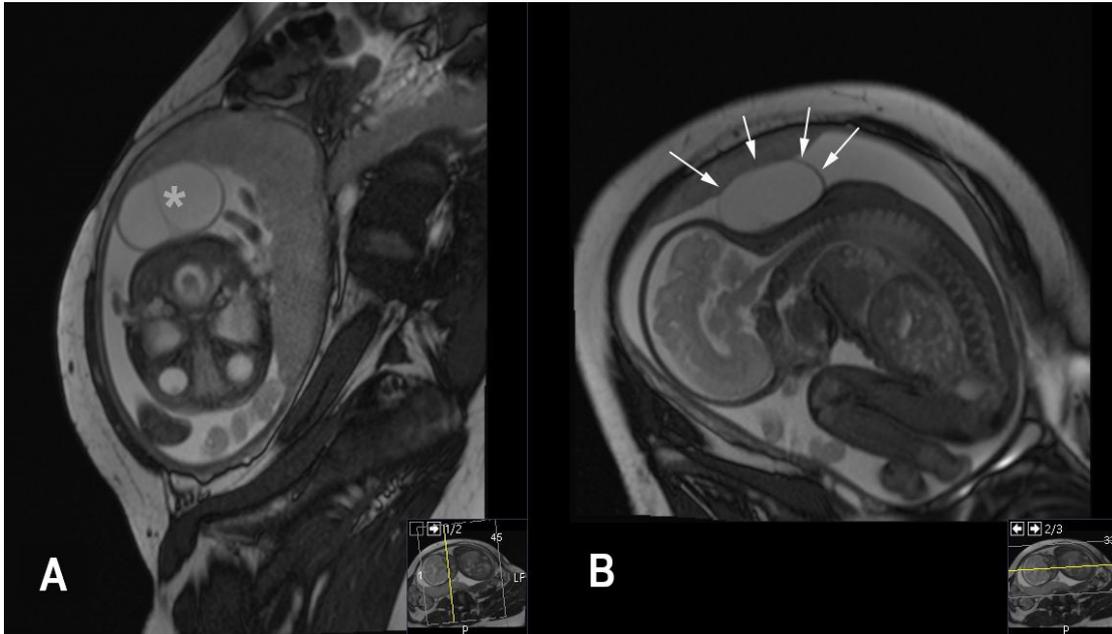
Figure 1: Fetal MRI. A: T2-weighted images, axial sections, The meningocele sac (Asterix). B: T2-weighted images, sagittal sections, The borders of the meningocele sac (Arrow).
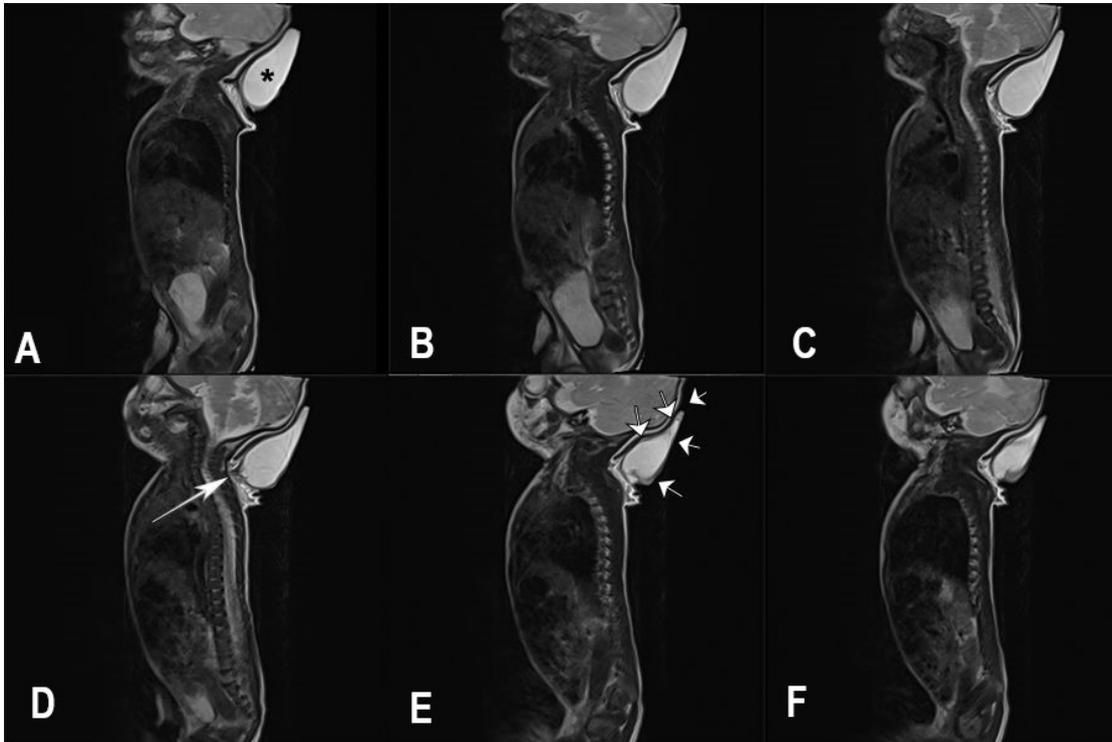
Figure 2: Neonatal MRI. A-F: T2-weighted images, sagittal sections. A: The meningocele sac (Asterix). D: The connection to the spinal canal (Arrow). E: Skin covering the meningocele sac (Arrows).
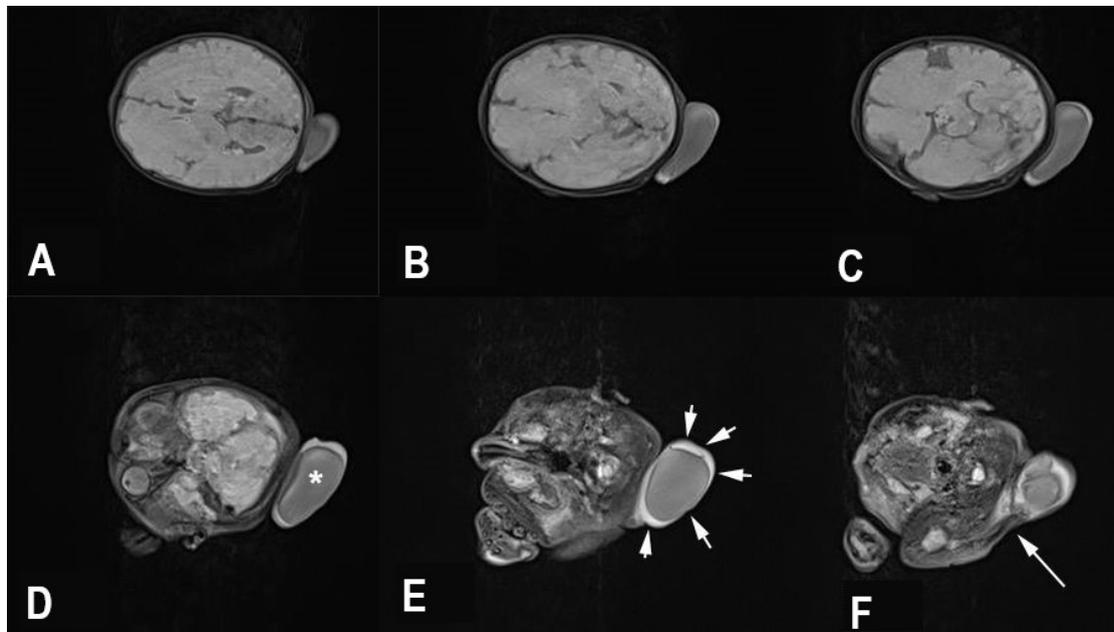
Figure 3: Neonatal MRI. A-F: T2-weighted images, axial sections. D: The meningocele sac (Asterix). E: Skin covering the meningocele sac (Arrows). F: The connection to the spinal canal (Arrow).
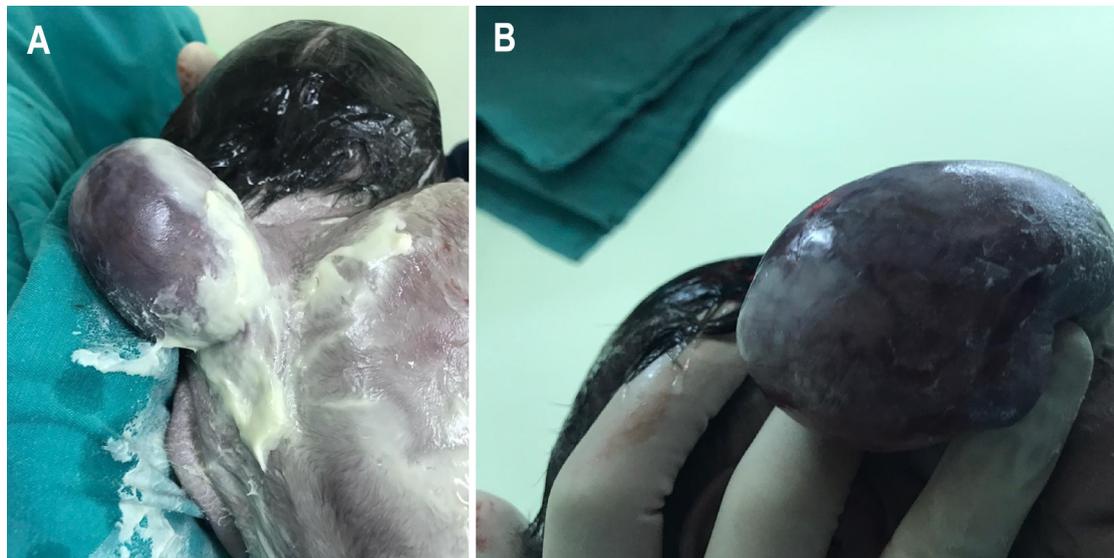
Figure 4: A,B: Preoperative pictures of the meningocele sac.

The baby was delivered by cesarean section, weighing 3.14 kilograms. The next day, he was taken to the operating room to have the cyst removed. Preoperative images of the cyst were given in Figure 4.

The infant was placed in a prone position. The cyst was opened with a ring-shaped incision and dissected by using dissecting scissors and cautery (Figure 5A). The dural layer and its borders were inspected, and a ring-shaped maneuver around it was made to remove the cyst (Figure 5B). Later, the paravertebral muscles were retracted to reach and cover the pathologic opening at the 7th cervical vertebra level (Figure 5C). Neural roots and the associated structures were collected inside (Figure 5D), and then dural layer was closed in a waterproof fashion, using 5-0 sutures (Figure 5E). Fibrin glue was applied. After meticulous hemostasis, the remaining layers were closed (Figure 5F).

There were not any complications in the postoperative follow-up. The patient was also examined after 6 months and no neurological deficits were detected.
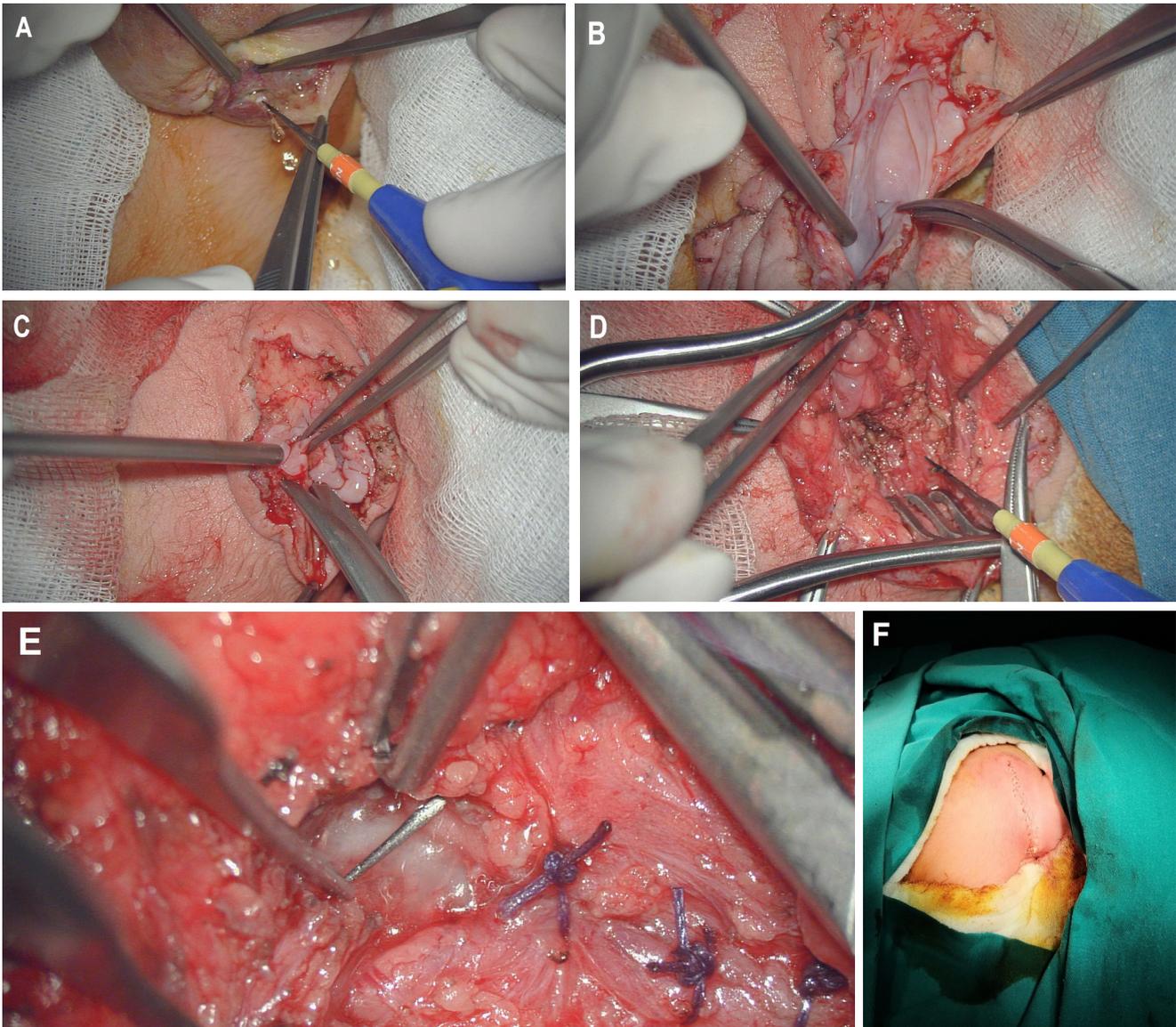
Figure 5: A-F: Pictures of the operation phases.

DISCUSSION

Spinal dysraphism is divided into two distinct categories. When planning a surgical involvement for such cases, the type of the lesion must be taken into consideration. In a case of spina bifida aperta, the neural canal is open, and the absence of a layer covering the neural tissue increases the risk of life-threatening complications such as infection and excessive loss of cerebrospinal fluid. These cysts should be removed as early as possible after birth (11). For spina bifida occulta cases, however, surgical procedure should be completed within 72 hours from birth and an MRI of the whole spinal column is recommended (12).

With proper surgical involvement, the prognosis for the newborn with cervical meningoceles is generally excellent (13). However, lesions should still be evaluated with care, as there may be underlying conditions such as hydrocephalus, syringomyelia, diastematomyelia, and tethered cord with progressive neurological deteriorations in the limbs (8, 13).

The removal of the lesion should be performed within the aforementioned time intervals, for early treatment is highly essential to prevent infection, sac injury and additional neurological defects that may occur in the future (13, 14). Erşahin et al. (13) reported that once the symptoms of tethered cord have developed, especially in the case of sphincter dysfunction, surgical involvement is unlikely to reverse the outcome. In another study conducted by Öncel et al. (14) the association between early surgical involvement and a shortened duration of hospital stay was highlighted. It was also

stated that early surgical involvement increases the likelihood of a maintained function of the urinary tract (14).

In our case, the surgical procedure was completed within the first 24 hours from birth. This will highly decrease the risk of aforementioned future anomalies, while. significantly improving the patient's overall health in the following years. It was made sure that no tethering was present by investigating the pathologic area at the seventh vertebra level. On the 6 months follow-up of our case, no neurological deficits were detected.

Konya et al. (15) presented a 47-year-old patient whose cervical meningocele was not treated upon birth and manifested symptoms in adulthood, such as fluid leakage from the sac which was infected, walking difficulty, stiffness in lower extremities and tethered cord syndrome. Although there was no recurrence in symptoms 12 months after surgery involving the excision of the cyst, it was noted that untreated tethered cord might pose a severe risk and careful assessment for possible tethering pathologies is vital (15).

In conclusion, regardless of the lesion's nature, a multidisciplinary approach involving the departments of pediatry, radiology, obstetrics and neurosurgery is needed for an effective treatment of cervical meningoceles. Post-surgical follow-ups are highly important to maintain a good prognosis in the long term. As in the rest of spinal dysraphism, early detection and prompt surgical involvement significantly improve the prognosis of cervical meningoceles.

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CORONAVIRUS DISEASE-19 (COVID-19): THE DISEASE THAT CHANGED THE WORLD

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ABSTRACT

In December 2019, several cases of severe pneumonia were identified in Wuhan City, the capital of Hubei province. Upon further investigation, the pathogen causing these symptoms was identified and named as SARS-CoV-2 and the disease was given the name COVID-19 by the World Health Organization. Being able to spread rapidly through respiratory droplets and capable of asymptomatic transmission, COVID-19 became a health concern of a global scale in a matter of months. The most common signs and symptoms of COVID-19 patients at hospital admission are fever, dry cough, and dyspnea. Most people experience the disease with mild symptoms but in more severe cases these can develop into pneumonia and acute respiratory distress syndrome. In this review, we aim to summarize the current information over COVID-19 and its causative agent SARS-CoV-2.
Keywords: COVID-19, SARS-CoV-2, pandemic

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by the most recently discovered severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) (1). The disease was first identified in December 2019 in Wuhan, Hubei Province in China as cases of pneumonia of unknown etiology (2). Most of the initial cases were epidemiologically linked to the Huanan seafood market (2, 3). Since the identification of early cases in Wuhan, the disease has spread rapidly throughout China in just a few months, inevitably turning into a national public health crisis. As patients presenting the same symptoms have gradually been documented in other countries, World Health Organization (WHO) recognized the outbreak as a Public Health Emergency of International Concern on January 30, 2020 (4). Taking the significant public health risks that the international spread of the disease poses to the world into consideration, the outbreak was declared as a pandemic on March 11, 2020 (5).

VIROLOGY

Coronaviruses are positive-sense single-stranded RNA genomes that are enveloped and non-segmented. They are 50-200 nm in diameter (6). Animals are the most common hosts for these viruses, but there are also a few cases in which humans were recorded as the hosts (7). The coronavirus family has four different genera: alpha (α), beta (β), gamma (γ), and delta (δ). Only α and β can infect humans (8).

Even though many human Coronaviruses (hCoVs) such as hCoV-229E, OC43, NL63, and HKU1 exist, there had only been two incidents of CoV infections managed to catch the world's attention before the latest outbreak: severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV). The SARS-CoV outbreak has occurred in 2002 infecting 8422 and causing 916 deaths. The first case of MERS-CoV infection occurred in 2012 and 543 of 1041 infected people have lost their lives due to the outbreak (8).

The SARS-CoV-2 is a zoonotic virus, similar to SARS-CoV and MERS-CoV. Primarily, the Coronaviridae Study Group (CSG) informed that these two viruses model a new species in a new unofficial subgroup of the group Betacoronavirus (1). They were granted specific names as they were the first ones to be identified in their species. SARS-CoV-2 is connected to a previously existing species with many acknowledged viruses usually isolated from humans and hosted by numerous bats. Since the human isolates collected during the 2002-2003 epidemic have been confirmed to

cause SARS in infected individuals, the names of all these viruses originated from SARS-CoV. The name SARS-CoV-2 was chosen by the CSG by using the entrenched method for identifying viruses in this species and the relationship of the virus to the model SARS-CoV in a species tree (1).

SARS coronavirus of 2002 (SARS-CoV) and SARS-CoV-2 are considered to be genetically identical. If these viruses find an animal reservoir that provides a cellular environment that is enough for them to multiply and get advantageous mutations, the virus can infect humans and multiply in human hosts (6).

ORIGIN AND SPREAD

In December 2019 several cases of severe pneumonia were identified in Wuhan City (9-12). Chinese authorities conducted an immediate investigation of the incident (11). Many of the initial cases were linked to the Huanan wholesale seafood market, in which alive animals such as poultry, dogs, snakes, bats, and fish are traded (9-12). A surveillance system was installed after further cases continued to share a common history of coming into contact with the market (9). On December 31, 2019, China alerted the WHO on the current outbreak. This was followed by the closure of the Huanan seafood market the next day (13). The causative agent was later described as a coronavirus that shared over 95% of its genome with a species of coronaviruses that was commonly found in bats (12, 14). Further investigations based on environmental samples indicated the seafood market as the origin of the disease (9). The exponential increase in the number of cases, some of which had never come into contact with the seafood market, indicated that human to human transmission was occurring (9, 11, 15).

On January 13, 2020, the first case outside of China was reported in Thailand (13). This was closely followed by the initial reports in South Korea and Japan. The occurrence of COVID-19 in these countries on people that have never been to China, supported the concern that the disease could be carried from human to human (15). On January 30, 2020, WHO declared the COVID-19 outbreak as a public health emergency of international concern, explaining that the rapid spread of the disease might pose a risk to the integrity of health systems around the world, especially for countries with vulnerable health systems (13). In the following months, COVID-19 continued to spread around the world. Due to its aggressive spread and high level of severity, COVID-19 was declared a pandemic by the WHO on March 13, 2020 (13).

EPIDEMIOLOGY

The SARS-CoV-2 has been spreading rapidly since December 2019 and as of April 27, there are 2,878,196 cases and 198,668 deaths according to WHO Situation Report-98 (16).

The source of the SARS-CoV-2 infection can be a previously infected person or object. It can spread by inhaling the droplets that are scattered via coughing and sneezing by infected people. The droplets larger than 60 μm in diameter are disposed to drop quickly (17). Furthermore, the virus may spread by one contacting surfaces that were infected and then touching their face, eyes, nose, or mouth before proper handwashing (18).

Individuals with COVID-19 usually begin to show symptoms, including mild respiratory symptoms and fever, 5-6 days after infection (19). The mean incubation period being stated; the incubation period of the SARS-COV-2 varies between 1-14 days (19). The virus can also get spread by asymptomatic patients (20).

Researches have shown that people of all ages can be infected by the SARS-CoV-2. However, older patients, immunocompromised patients, and patients with serious underlying medical conditions such as diabetes, severe obesity (body mass index of 40 or higher), pulmonary diseases, liver diseases, and patients with chronic kidney disease undergoing dialysis are in the high-risk group (21, 22). In a study reported by Garg et al. (22) between March 1 and 30, 89.3% of 178 hospitalized adults had at least one underlying condition. Hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%) ranked among the most common underlying conditions. While among the patients aged 18-64 obesity was the most frequent underlying condition, among those aged ≥65 years' hypertension ranked first. In the meantime, hospitalization rates increase with age and 74.5% of 1482 hospitalized patients were aged ≥50 years (22).

PATHOGENESIS

The causative agent of COVID-19 is a virus called SARS-CoV-2 (23). The same genome structure and expression pattern are seen among all coronaviruses. They encode 16 nonstructural, 4 major structural [spike (S), envelope (E), membrane (M), and nucleocapsid (N)] proteins (24). S protein binds to the receptors on the host cell, thereby helping the virus enter the host cell, and is critical for determining transmission capacity and host tropism (25, 26). Angiotensin-converting

enzyme 2 (ACE2) receptor in the respiratory mucosa is one of these receptors (27). According to the literature, 8 of the 14 binding residues directly interacting with human ACE2 in the SARS coronavirus (SARS-CoV) have been preserved in SARS-CoV-2 (28). In addition, the S protein produced by SARS-CoV-2 was found to have a 10 to 20-fold higher binding affinity to human ACE2 than the S protein of SARS-CoV (29).

After the virus enters the cells, the viral RNA genome is released into the cytoplasm and the viral genome begins to replicate. Two polyproteins and structural proteins are produced and the newly formed envelope glycoproteins enter the membrane of the endoplasmic reticulum or Golgi apparatus (30). The nucleocapsid is formed by the combination of genomic RNA and nucleocapsid proteins (31). The viral particles then develop into the Endoplasmic Reticulum-Golgi intermediate compartment (ERGIC) (31). Finally, the vesicles containing the virion fuse with the plasma membrane and release the virus (31).

Fever, dyspnea, nonproductive cough, pneumonia, myalgia, fatigue, normal or decreased levels of leukocytes, increased levels of plasma pro-inflammatory cytokines are among the clinical signs of patients with SARS-CoV-2 infections (15, 32). Symptoms of COVID-19 are similar to the symptoms of SARS-CoV and MERS-CoV infections (33). The pathogenesis of the disease is mainly presented with severe pneumonia, RNAaemia, ground-glass opacities, and acute cardiac injury (15).

According to the literature, ARDS has been found as the common result of SARS-CoV-2, SARS-CoV, and MERS-CoV infections and is the main cause of death (15, 34). Cytokine storm, the overproduction of cytokines by the immune system, causes a violent attack on the body, triggering ARDS and multi-organ failure, subsequently leading to death in severe cases of SARS CoV-2 infections, as in SARS-CoV and MERS-CoV infections (15, 34-37).

Patients with COVID-19 showed significantly high blood levels of cytokines and chemokines including IL1-ß, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA (15). Furthermore, plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα were shown to be higher in the Intensive Care Unit (ICU) patients than non-ICU patients (15). In addition, according to recent reports, the number of CD4 + and CD8 + T cells in peripheral blood of SARS-CoV-2 infected patients are significantly reduced (34).

The pathophysiological mechanisms under the emergence of SARS-CoV-2 have not been fully understood.

However, the genomic similarity of the causative pathogen SARS-CoV-2 with SARS-CoV and MERS-CoV may facilitate the recognition of the COVID-19 and help explain the inflammatory response causing the clinical outcomes with severe pneumonia (28).

CLINICAL PRESENTATION

The most common signs and symptoms of COVID-19 patients at hospital admission are fever, dry cough, and dyspnea. Other symptoms may consist of fatigue, myalgia, headache, sputum production, and sore throat (38-40). Some case series reported the existence of gastrointestinal symptoms in 2-40% of the patients (39, 41). In comparison, gastrointestinal symptoms such as diarrhea are less common, which shows that its viral tropism is different in comparison with MERS-CoV and SARS-CoV (39).

Three non-peer reviewed expert body press releases from the United States of America, United Kingdom, and France suggested that based on anecdotal emerging clinical observations, changes in olfactory sensations such as anosmia and hyposmia could be clinical features of COVID-19, especially in early or mild cases (42-44). Olfactory or taste disorders were recorded in up to 53% of the cases in a study from Italy (45). Although the preliminary current evidence for anosmia and hyposmia to be considered as potential clinical features of COVID-19 is inconclusive at the moment, they are proposed as new criteria for testing, especially in young people with few other symptoms (40).

According to the literature, the median incubation period was estimated to be 5.1 days and people may develop symptoms 2-14 days after the exposure to the virus (46, 47). Furthermore, the study conducted by Lauer et al. (46) has stated that 97.5% of infected people show symptoms in 11.5 days.

According to a study of case series from China, the most common laboratory abnormalities observed among their patients were elevated lactate dehydrogenase, depressed total lymphocytes, and prolonged prothrombin time (48). The laboratory abnormalities imply that SARS-CoV-2 infection may correlate with hepatic, renal and myocardial injury, coagulation activation, and immune deficiency. These abnormalities were found to be similar to the abnormalities that were seen at patients infected with MERS-CoV and SARS-CoV (48).

Another study of case series conducted by Huang et al. (15) has found abnormalities in the chest CT images of all patients. Furthermore, 98% of the patients infected with the virus presented with bilateral involvement,

and all patients in the study had pneumonia (15).

The common complications among patients included Acute Respiratory Distress Syndrome (ARDS), acute cardiac injury, RNAaemia, and secondary infections (15). Coinfections of fungi and bacteria were seen in especially severely ill patients (49). Some patients progressed with ARDS and septic shock, which was ultimately followed by multiple organ failure (15, 49).

In the course of the disease, the median duration from the inception of the first symptoms to developing dyspnea was 5.0 days, 7.0 days to hospital admission, and 8.0 days to developing ARDS, and for discharged patients, the hospital stay was recorded as 10 days (48).

DIAGNOSIS

WHO describes COVID-19 patients in three separate case definitions: a suspected case is defined as a patient that shows at least one symptom of acute respiratory illness along with fever and has a history of residence in or travel to a location with reports of community transmission of COVID-19 in at least two weeks prior to symptom onset, or a patient with acute respiratory illness and is yet to receive an alternative diagnosis that fully covers the clinical findings (50). A probable case is described as a suspected case for whom the laboratory tests are reported inconclusive or a suspected case for whom testing could not be performed (50). A case can only be defined as positive when a person's laboratory tests return positive for the SARS-CoV-2 infection (50).

Nucleic acid detection in respiratory tract samples in a real-time polymerase chain reaction (RT-PCR) and next-generation sequencing is the forerunning and the most essential method of SARS-CoV detection, in virtue of its commercial viability and relatively short return time (51, 52). Specific probes and primers were designed, utilizing the genome sequence of the virus to help accelerate the development of RT-PCR diagnostics (53). The first open reading frames (ORF 1a and 1b), RNA-dependent RNA polymerase gene, envelope, and nucleocapsid are the main focus for novel coronavirus detection and diagnosis at the moment (51, 53). Many in-house assays have been developed or are under development (54). However, this method is not without its shortcomings since RT-PCR has high false-negative rates as well as low detection rates. Furthermore, RT-PCR cannot be used to determine the progression or the severity of the disease (52, 55, 56). In addition, the collection of nasopharyngeal, oropharyngeal samples requires close contact between the patient and the healthcare worker which may lead to further transmission of the disease (57).

Chest X-Rays (CXR) usually do not give specific results as bilateral infiltrates seen in CXR may be normal in early disease (58). Another detection method is computed tomography (CT), which is more sensitive and plays an important role in the clinical detection of COVID-19 (55, 56). Ground glass opacities in multifocal lung lesions are typical findings from chest CTs of COVID-19 patients. Investigations of such common symptoms appear to have higher rates of detection than the nucleic acid tests, as well as having the ability to see the severity and track the progression of the disease (52). However, CTs are not commercially viable and not able to identify the specific virus causing the symptoms (55).

Antibody assays can also be an actor in the diagnosis of the COVID-19, albeit as complementary for the viral nucleic acid test (59, 60). The primary method of antibody tests is enzyme-linked immunosorbent assay (ELISA) and studies have shown that IgM, IgG, and IgA antibodies can be observed as early as four days after symptom onset. Detection by IgM seroconversion led to higher rates of accurate diagnosis than those of PCR assays five days after symptom onset (59). The detection rates increased significantly when IgM ELISA assay was applied along with a PCR test for each patient (59, 60).

CLINICAL MANAGEMENT

Although patients experiencing mild symptoms do not necessarily need hospital admission, it is still very important to implement applicable infection prevention and control measures in order to contain transmission (61). Following the doctors' and health care guidelines' recommendations, this could be done either in the hospital or at home. Patients with mild illness may be treated with symptomatic treatments such as prescribing antipyretics to manage their fever (61).

When it comes to patients with hypoxemia, severe acute respiratory illness (SARI) and respiratory distress, or shock, these patients should be provided with supplemental oxygen therapy immediately (61). Adults with emergency signs such as absent or obstructed respiration, central cyanosis, severe respiratory distress, shock, convulsions, or coma have to receive airway management and oxygen therapy (61). Patients with COVID-19 should be monitored closely for signs of clinical deterioration and should be intervened with attainable supportive care instantly if necessary (61). The vital signs of patients that have been admitted to the hospital need to be observed consistently. Early warning scores may be used to determine the status

of the patients and can be beneficial to recognize the deterioration of their condition (62). It is important to keep in mind that aggressive fluid resuscitation might worsen oxygenation, therefore health care staff should be careful while administering patients with SARI with intravenous fluid treatments (63). It is also crucial to consider that patients with ARDS might still experience hypoxemia even when oxygen is delivered with a mask accompanied by a reservoir bag (61).

Deterioration into septic shock is very dangerous, therefore all patients should be monitored closely in order to recognize the signs of septic shock and get ahead with early interventions. The advised care for septic shock patients includes antimicrobial treatment, fluid bolus therapy, and implementing vasopressors within the first hour of septic shock recognition (64).

Taking into account that asymptomatic transmission of the disease may also occur among pregnant and/or recently pregnant women, health care professionals should observe all women who have a history of contact thoroughly (61). All pregnant women recently diagnosed or women who have recovered from the disease shall be given necessary instructions regarding how to feed their infants safely and regarding appropriate measures to prevent transmission (61).

There have been comparably fewer cases reported of infants as confirmed cases. Additionally, infected infants have reportedly experienced mild symptoms (61). According to the literature, there is not yet any documentation of vertical transmission (61). According to the data from WHO, amniotic fluid sample from six mothers who were positive for SARS-CoV-2 were all negative for the virus. Moreover, the throat swabs and cord blood taken from their neonates also tested negative for the virus (61). Furthermore, the samples that were taken from the mothers' breast milk after the primary lactation were all negative for the virus (65, 66). Mothers whom are considered as suspected, probable, or confirmed cases, should feed their infants consistently in accordance with the advised guidelines for feeding their infants while taking necessary precautions to prevent any transmissions (61).

PROGNOSIS

Intensive care unit

A study comprising 138 hospitalized patients revealed that organ dysfunction developed in approximately 25% of the patients who were later transferred to the ICU (48). Patients admitted to the ICU have been reported to have a higher median age and to be more likely to have underlying diseases such as diabetes or hypertension, compared to patients who did not receive intensive care (48).

Patients treated in the ICU were found to be more likely to have pharyngeal pain, dyspnea, dizziness, abdominal pain, anorexia, and many laboratory abnormalities, compared to patients that have not been admitted to the ICU (48).

Several complications may occur in critical patients who receive intensive care as the disease progresses. These complications include ARDS, acute cardiac injury, shock, arrhythmia, acute kidney injury, secondary infections, and RNAaemia (15, 48).

Comorbidities

The elderly and people with underlying comorbidities are the main risk groups for having poor prognosis (48, 67). In a study with COVID-19 patients, Wang et al. (48) stated that 46.4% of patients had one or more accompanying medical conditions including hypertension (31.2%), cardiovascular disease (14.5%), diabetes (10.1%) and malignancy (7.2%).

Lippi et al. (68) have found that patients with hypertension had approximately 2.5 times higher risk of developing a severe illness or risk of mortality, especially in older individuals. In addition, the chronic obstructive pulmonary disease has been found to carry more than a 5-fold higher risk of severe illness or death and chronic kidney disease more than 3-fold higher risk (69, 70).

Elderly people

The median duration from the onset of the first symptoms to death of patients over 70 years old is 11.5 days, which indicates the vulnerability of the elderly towards SARS-CoV-2 (71). If a patient is not considered old or immunocompromised, the patient may not develop fever, which is one of the most typical symptoms of COVID-19 (72).

Chen et al. (49) have conducted a study on 99 patients with COVID-19 and found that older men with comorbidities are more likely to be affected by   COVID-19, leading to serious and even fatal respiratory diseases such as ARDS.

The response of the immune system to previously exposed pathogens is more conserved than its response to never-exposed pathogens. On the contrary, there is a large number of pure T cells ready to be educated by new pathogens in children who have encountered relatively few pathogens. This may explain the more severe

course and higher mortality of COVID-19 in the elderly compared to children (73).

As a result, if the innate immune system fails to produce an adequate adaptive response (i.e. virus-specific CD8 + T cells), it can be said that persistent self-induced inflammation can cause mortality in risk groups such as the elderly, with associated comorbidities or immunosuppressed (73).

Children

Children are susceptible to respiratory system infections because their immune system is yet immature, which results in more diverse symptoms. Therefore, issues like the formation of antibodies or cross-immunity can be easily overlooked (74). SARS-CoV-2 is mainly transmitted among children by close contact and respiratory droplets, similar to adults (74).

It has been reported that COVID-19 progresses significantly milder in neonates, infants, and children compared to adults (9). In a study conducted on 34 children, all the patients were either asymptomatic (9%) or had mild symptoms, and there were no critical cases or deaths. Fever (50%) and cough (38%) were the most common symptoms, and all patients recovered with symptomatic treatment (75). However, with the spread of the outbreak, the number of infected children has increased gradually (74). There have also been critical cases among children, one of these cases were reported in China, describing a child with severe pneumonia and multiorgan dysfunction (76).

Pregnant women

Pregnant women are more susceptible to respiratory pathogens, and due to high levels of estrogen and progesterone during pregnancy, the upper respiratory tract tends to swell (77).

In addition, pregnant women are in the pro-inflammatory state especially in their first and third trimester, therefore, cytokine storm caused by COVID-19 can lead to a more severe inflammatory condition (78). Although current evidence does not support intrauterine ventral transmission, perinatal SARS-CoV-2 infection can affect the developing fetus and postpartum life (66, 77). Perinatal COVID-19 may also have negative consequences such as abortion, fetal growth restriction, preterm birth, premature rupture of membranes, fetal distress, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and maternal death (65, 66).

Further efforts should be made to protect both mothers and fetuses during the ongoing outbreak. In the first and second trimesters, it is necessary to investigate pregnant women with COVID-19 and carefully monitor all infected women during pregnancy and after birth (77).

PREVENTION

In the fight against COVID-19, exercising necessary precautions is highly crucial in order to contain the spread of infection. Social distancing, self-isolation, hand washing, surface cleaning, and use of personal protective equipment are some of these measures (79, 80).

SARS-CoV-2 is a virus that is mainly transmitted through close contact and respiratory droplets. High-risk groups, especially older people and those with chronic diseases, should avoid public places to protect themselves. It is also important for everyone to maintain a social distancing of at least 1 meter (81). Hands must be washed at least 20 seconds after being in public areas or touching surfaces possibly containing the virus. If water and soap are not accessible, hand sanitizer that includes at least 60% alcohol is recommended (80).

Quarantine is used to keep someone who might have been affected by the SARS-CoV-2 away from others. As for isolation is used to separate sick people from healthy people. Some individuals may not show symptoms even though they are sick. Individuals in this situation may cause the disease to spread without realizing it (82). Those who are carriers or potential carriers of the disease should remain in quarantine. These individuals should be detected and isolated immediately (82).

Another issue is face masks, coverings, and their usage. Taking the highly contagious nature of the disease into consideration, it is advised for everyone to use face coverings in public places (80). This will help to protect other people from sick and/or asymptomatic individuals. Masks, especially high-level masks like the N95, are recommended to be reserved for healthcare workers since they are in more direct contact with sick people compared to the general population (83). Even though the usage of face masks is advised for the public, it is important to emphasize that face masks do not provide full protection and can even increase the risk of infection if not used properly (84).

Healthcare workers have an increased risk of being infected with the virus. Therefore, all healthcare workers require full personal protective equipment including a face shield, isolation gown, gloves, and mask. Medical applications such as tracheostomy, tracheal

intubation, bronchoscopy, open airway suctioning, high flow oxygen therapy, and autopsy are considered as aerosol-generating medical applications (85). While performing an aerosol-generating medical procedure, the N95 mask must be used. The N95 masks prevent 95% of droplets from entering through the mask and significantly decrease the risk of getting infected (85).

CONCLUSION

According to the Situation Report of the WHO that was released on 27 April 2020, there are nearly 3 million confirmed cases and approximately 200.000 deaths due to the COVID-19 pandemic. The United States of America is the country with the most confirmed cases and highest death rates according to the current data (16).

The studies for the development of a vaccine are still ongoing. The research and development landscape of the global COVID-19 vaccine contains 115 candidates. According to the literature, 78 of those candidates are confirmed as active and 37 are yet to be confirmed. In addition, 73 of the 78 confirmed active projects are currently at exploratory or preclinical stages. Besides, many others declared plans to start human testing in 2020 (86).

There are some simple but effective steps to follow offered by WHO to stop the spread of COVID-19 around the world. Those steps are washing hands frequently, maintaining social distancing of at least 1 meter to avoid droplets from coughs and sneezes, averting touching eyes, nose, and mouth and practicing respiratory hygiene which means covering your mouth and nose with your bent elbow or tissue when coughed or sneezed and discarding of the used tissue. The last step to follow is if you have shown all of the symptoms, you should seek medical care immediately. The point of this is to avoid a lethal outcome for yourself and to restrict the circulation of the virus (81).

In the past 50 years, there have been many cases of coronaviruses affecting humans and animals and it is highly possible that new types of coronavirus will emerge in the future (87). To overcome the burdens and outcomes of such infectious diseases, open communication, and collaboration among the international community are highly essential. In conclusion, the COVID-19 pandemic emphasizes the importance of public health management, investment in scientific research, and the immense need for global cooperation.

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POSSIBLE BENEFICIAL EFFECTS OF VITAMIN K AND OSTEOCALCIN ON GLUCOSE METABOLISM

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ABSTRACT

The role of vitamin K, in bone metabolism and its effects on insulin resistance and Type-2 diabetes, have been discussed. The mechanism of vitamin K's beneficial effect on insulin sensitivity and glucose homeostasis is not yet known. Various biological active molecules such as adiponectin, leptin, and resistin, which is secreted from adipose tissue and have important roles in glucose metabolism, have been proposed to regulate bone metabolism. Some studies have suggested that bone metabolism is also effective on adipose tissue and energy metabolism. It is thought that osteocalcin, a vitamin K dependent protein is effective in glucose metabolism. The role of Vitamin K in glucose metabolism is thought to be partly due to the modulation of diabetes-related cytokines and other metabolic risk markers, as inflammation lies at the bottom of chronic metabolic diseases. The aim of this review is to explain the effect of Vitamin K and osteocalcin on glucose metabolism and its possible mechanisms of action.

Keywords: Vitamin K, osteocalcin, glucose metabolism, type 2 diabetes, insulin resistance

INTRODUCTION

Micronutrients have been received as a supplement to health promotion and disease prevention after recognizing their important role in the management of diseases (1). Even moderate deficiencies of micronutrients, which usually act as coenzymes or cofactors in metabolic activities in our bodies, cause serious health problems (1, 2). In recent years, it has been determined that micronutrients have a therapeutic effect on many chronic diseases including diabetes (3, 4).

The crucial role of Vitamin K in blood coagulation is well known (5). Carl Peter Henrik Dam (6) who discovered Vitamin K, to symbolize its ability to coagulate, named the vitamin as "K". Vitamin K has two natural forms: phylloquinone (Vitamin K1) and menaquinone (Vitamin K2) (2, 7). Phylloquinone, the most important form of dietary Vitamin K, is found in many vegetable oils, fruits, dairy products, and cereals as well as green vegetables (2). While the most important sources of menaquinone in dietary intake are meat, cheese, and eggs, it is mainly produced by intestinal bacteria (8). Besides, phylloquinone can be converted to menaquinone-4 (9). Furthermore, vitamin K functions as a cofactor for γ-glutamyl carboxylase enzyme which is essential for the vitamin K dependent proteins (9).

Previous studies have focused on the role of Vitamin K in blood coagulation (5, 6). Besides its role in blood coagulation, Vitamin K improves bone health, prevents vascular calcification, and reduces the risk of cardiovascular diseases (10–12). Furthermore, it is considered to have beneficial effects against insulin resistance (13). Recent studies have shown that Vitamin K increases insulin sensitivity, improves glucose metabolism, and reduces the risk of Type-2 diabetes mellitus (14–18). In a study conducted by Ertaş-Öztürk et al. (19) Vitamin K and glucose metabolism of non-obese healthy individuals were investigated. It is determined that dietary Vitamin K intake may have a protective effect on insulin resistance. However, another study showed that glucose tolerance was not improved by seven days of Vitamin K supplementation (20). The association between Vitamin K and Type-2 diabetes mellitus and the way it possibly uses to prevent insulin resistance are unclear. This review aims to explain the effect of Vitamin K on Type-2 diabetes mellitus and its potential mechanisms.

The Relationship Between Glucose Metabolism and Vitamin K

Diet and lifestyle play an important role in the progression of insulin resistance, a metabolic disorder in which hepatic and peripheral tissues are less susceptible to insulin (21). In recent years, there have been studies proposing that Vitamin K intake or deficiency was related to insulin resistance (14–16). The mechanism of vitamin K on insulin sensitivity and glucose homeostasis are not yet known (2). Various biological active molecules such as adiponectin, leptin and, resistin (22-24), which are secreted from adipose tissue and have important roles in glucose metabolism, have been proposed to regulate bone metabolism. Some studies have suggested that bone metabolism is effective on adipose tissue and energy metabolism (25, 26). Many studies have suggested that osteocalcin which is a vitamin K dependent protein, is effective in regulating glucose metabolism (9, 15, 25). It has been determined that osteocalcin stimulates β-cell proliferation, insulin secretion, and insulin sensitivity by stimulating adiponectin secretion (25).

Bone and glucose metabolism are linked by a complex metabolism that contains leptin, osteocalcin, and adiponectin (27). The possible effects of Vitamin K intake and osteocalcin on glucose metabolism are shown in Figure 1.

Osteocalcin is a Vitamin-K dependent protein synthesized by osteoblasts (7). It has been thought that osteocalcin is the most common non-collagen protein in the bone and its concentration is positively correlated with osteoblast function and Vitamin K availability (12). Vitamin K acts as the cofactor of the gamma-glutamyl carboxylase enzyme which is essential for the synthesis of osteocalcin (Figure 2). Osteocalcin contains a propeptide recognition site for binding gamma-carboxyglutamate (13). After carboxylation, the propeptide is separated and active osteocalcin is synthesized (28). Gamma-carboxyglutamate residues in the osteocalcin are responsible for the shape, size, and bone metabolism of the bone mineral (7, 10).

Studies have described three forms of osteocalcin: carboxylated, uncarboxylated and undercarboxylated osteocalcin (7). The difference between uncarboxylated and undercarboxylated osteocalcin has not yet been clearly explained. However, it has generally been reported that high serum undercarboxylated or uncarboxylated osteocalcin is associated with the low levels of Vitamin K (10). Although changes in the concentration of undercarboxylated osteocalcin have been reported not to affect glucose metabolism, many researchers have reported that the active form of osteocalcin is undercarboxylated (7, 27). It was reported that Vitamin K supplementation (K1 or K2) decreased the level of non-carboxylated osteocalcin, increased the level of carboxylated osteocalcin, and reduced insulin resistance in patients with the high risk of Type-2 diabetes (10). As a result of a study of 348 non-diabetic men and women for three years, Shea et al. (29) reported that uncarboxylated osteocalcin was not associated with higher insulin resistance whereas low carboxylated osteocalcin was associated with higher insulin resistance. However, Hwang et al. (30) suggested that both carboxylated and non-carboxylated osteocalcin levels improved glucose tolerance.

Lee et al. (31) investigated the endocrine regulation of energy metabolism by the skeleton. In that study, the osteocalcin gene was inactivated in mice. Visceral fat accumulation was impaired and the hyperglycemic state and impaired glucose tolerances were due to insulin resistance and insulin deficiency. It was found that osteocalcin increased beta-cell proliferation, insulin release, and sensitivity by stimulating insulin and adiponectin in beta-cells and adipocytes. Mice that could not produce osteocalcin were found to be obese, had low beta-cell proliferation, and developed insulin resistance (31). In another study, Vitamin K2 supplementation at different doses in rats during 8 weeks period increased the expression of osteocalcin, insulin 1, insulin 2, cyclin D2, which are the indicators of B-cell proliferation (32). Some amino acids and sizes of osteocalcin in mice and humans are different (27, 33). The roles of osteocalcin in glucose metabolism in in-vitro and in-vivo studies should be supported with human studies. Human and animal studies should be examined together to make a general conclusion. Table 1 summarizes human and animal studies investigating the effects of vitamin K and/or osteocalcin on glucose metabolism.
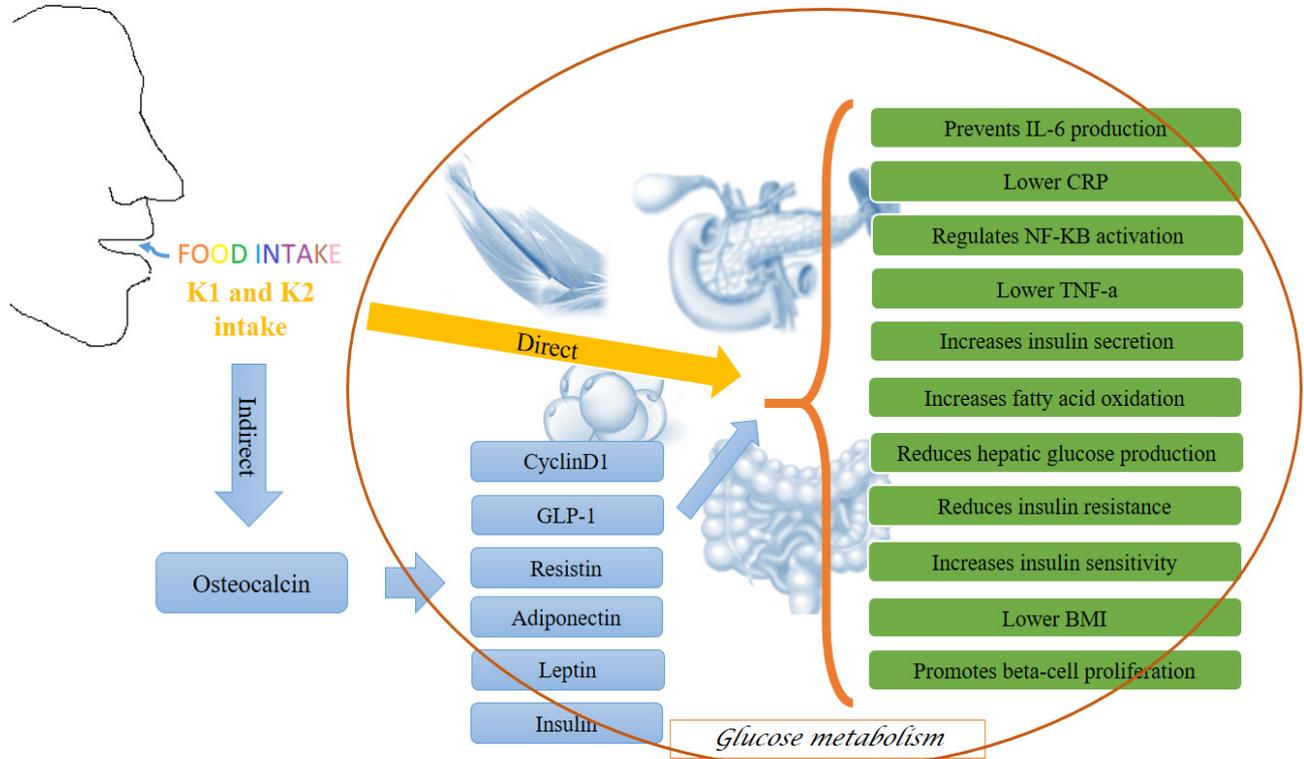
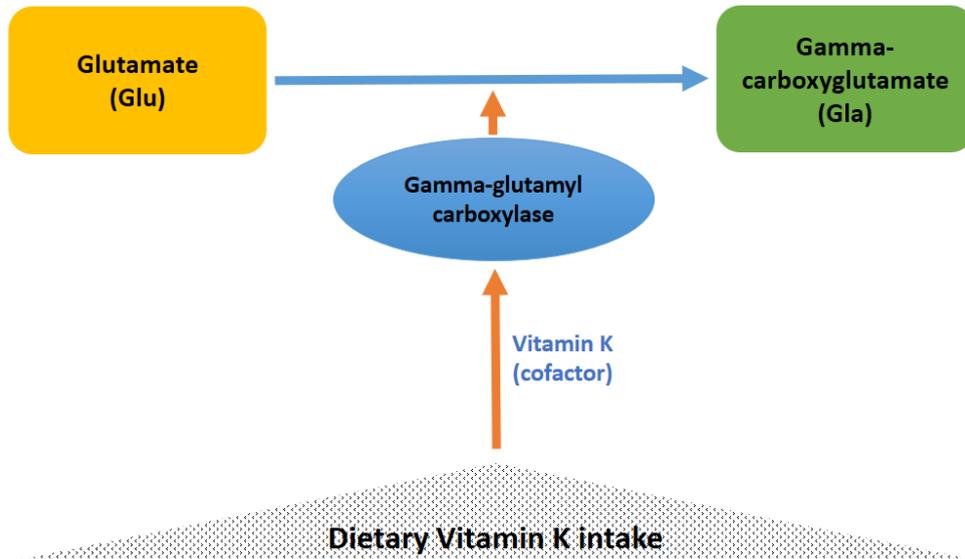*Figure 1: Possible direct and indirect mechanisms of Vitamin K and osteocalcin on glucose metabolism.*

Figure 2: Vitamin K is a cofactor for gamma-glutamyl carboxylase.

Table 1: Effects of Vitamin K and/or osteocalcin on glucose metabolism.

Study	Participants and design	Outcomes
Beulens et al. (14)	The levels of intake of Vitamin K1 and Vitamin K2 were evaluated by food frequency questionnaire which was questioned for the last 1 year of 38 094 Dutch men and women aged 21-64 years.	Each 10-mcg increment of menaquinone intake was associated with a 7% decrease in the risk of Type 2 diabetes.
Ibarrola-Jurado et al. (15)	2353 male diets were followed for a mean of 5.5 years.	The dietary intake of phylloquinone every 100 mcg/day was associated with a 17% lower incidence of diabetes.
Kumar et al. (16)	During postmenopausal period, 1 mg/day phylloquinone supplementation was performed for 12 months.	There was no significant difference in fasting blood glucose, insulin concentration and HOMA-IR levels in the control group.
Rasekhi et al. (17)	In a randomized controlled study of 82 prediabetic women supplemented with Vitamin K1 for 4 weeks.	According to the control group, fasting blood glucose and insulin concentration were lower in patients who received supplemental treatment, but insulin resistance (HOMA-IR) was not affected.
Yoshida et al. (18)	Dietary Vitamin K intake of 2719 individuals was evaluated by the food frequency questionnaire.	Higher phylloquinone intake was determined to have higher insulin sensitivity and better glycemic control.
Saleem et al. (26)	Serum osteocalcin levels of 1209 white people and 1284 black people were measured.	There was a relationship between serum osteocalcin levels and BMI, fasting blood glucose, insulin resistance, leptin, and adiponectin levels, which had a statistically significant difference.
Shea et al. (29)	348 non-diabetic individuals were followed for three years.	Higher levels of carboxylated osteocalcin were associated with lower fasting blood glucose, insulin resistance, and higher adiponectin levels.
Hwang et al. (30)	Serum osteocalcin levels of 199 men were measured.	Increased levels of both carboxylated and non-carboxylated osteocalcin were found to improve glucose tolerance in patients with impaired glucose tolerance.
Hussein et al. (32)	Vitamin K2 supplementation was performed at different doses to 30 rats for 8 weeks.	Osteocalcin, insulin 1, insulin 2, Cyclin D2 expressions were determined to increase.
Sakamato et al. (34)	Dietary Vitamin K intakes of individuals were determined by food frequency questionnaire.	The group receiving low dietary phylloquinone intake had lower insulin and higher blood glucose concentration.
Yoshida et al. (35)	In a randomized, double-blind controlled study, the elderly and non-diabetic 355 individuals underwent phylloquinone supplementation for 36 months.	HOMA-IR levels were found to be lower in the elderly than in the control group.
Pittas et al. (36)	Serum osteocalcin levels of 380 individuals over 65 years of age were measured.	Serum osteocalcin concentration was strongly correlated with plasma fasting glucose, insulin resistance, IL-6, body mass index (BMI) and body fat.
Pollock et al. (37)	Osteocalcin levels of 140 overweight prepubertal children with prediabetes and normal glucose levels were measured.	Low osteocalcin levels were found to be related to B-cell dysfunction in children with prediabetes.
Asemi et al. (38)	Vitamin D, Vitamin K and calcium (Ca) were supplemented to 66 diabetic patients.	Insulin concentrations, insulin resistance (HOMA-IR) and β-cell function were significantly different from the placebo group.
Choi et al. (39)	Menakinon-4 supplements were administered to 42 healthy adults.	In the K2-supplemented group, the level of carboxylated osteocalcin increased and insulin sensitivity improved compared to the placebo group.
Juanola-Falgarona et al. (40)	Dietary Vitamin K intake of 510 elderly people was followed for a year.	Diabetes-related inflammatory cytokines in those who increase dietary intake of Vitamin K decreased.
Varsha et al. (41)	Rats with Type-1 DM were supplemented with Vitamin K1 twice a week for 3 months.	Activation of proinflammatory genes and beta-islet necrosis were prevented. Beta-cell proliferation is facilitated.
Liang et al. (42)	1049 non-diabetic and 983 participants followed for four years.	People with impaired glucose metabolism have low osteocalcin level.

In epidemiological studies, dietary or supplementary intake of Vitamin K has been shown to reduce insulin resistance and improve glycemic levels (29, 34, 36, 37). Sakamoto et al. (34) evaluated the insulin responses depending on the intake of Vitamin K in the diet of participants who have normal body weight. It was determined that the group receiving low phylloquinone had lower insulin and higher blood glucose concentration. In a study conducted by Beulens et al. (14), each 10-mcg increase of menaquinone intake with diet was associated with a 7% reduction in the risk of Type-2 diabetes. The effect of vitamin K on glucose metabolism has often been associated with osteocalcin.

Low osteocalcin level is a risk factor for impaired glucose metabolism and Type-2 diabetes (42). However, in a study, no correlation was found between osteocalcin and glucose levels in patients with normal glucose tolerance (35). These studies demonstrate that the level of osteocalcin is closely related to glucose metabolism.

In a study performed by Saleem et al. (26), a significant relationship was found between serum osteocalcin levels and BMI, fasting blood glucose, insulin resistance, leptin, and adiponectin levels. Another study on older people showed that serum osteocalcin levels were associated with glucose metabolism, serum osteocalcin concentration was strongly correlated with plasma fasting glucose, insulin resistance, IL-6, body mass index and body fat (36). Pollock et al. (37) reported that osteocalcin is associated with glucose metabolism, and this relationship is associated with beta-cell functions. This study was conducted on prepubertal children. Although these studies focused on different age groups, the results were found to be compatible with each other. Not only cross-sectional studies, but also longitudinal studies showed that Vitamin K and osteocalcin were effective in glucose metabolism. In a long-term follow-up study, dietary intake of 100 mcg/day was associated with a 17% lower incidence of diabetes (15). In another follow-up study showed that low osteocalcin level was associated with impaired glucose metabolism (42). The strong relationship between vitamin K, osteocalcin, and glucose metabolism has been supported by these longitudinal studies.

Studies evaluating dietary vitamin K intake have shown beneficial effects on glucose metabolism. In addition to dietary intake, there are studies evaluating vitamin K intake as a supplement. In a recent study, 66 diabetic patients received Vitamin D, Vitamin K, and calcium supplementation. In this randomized, double-blind, placebo-controlled study, it was determined that insulin concentrations, insulin resistance (HO-MA-IR) and β-cell function showed significant differences compared to the placebo group (38). Choi et al. (39) evaluated insulin sensitivity by giving menaquinone-4 supplements to healthy young men for 4 weeks. It was determined that the level of osteocalcin and insulin sensitivity were higher than the placebo group in the supplemented group.

Since various forms of vitamin K are used, these studies are open to interpretation. In Rasekhi et al.'s study (17) Vitamin K1 supplementation was given to prediabetic women for 4 weeks. According to the control group, the fasting blood glucose levels and the insulin concentration were lower but the insulin resistance (HOMA-IR) was not affected. In another study conducted on 21 women during the postmenopausal period, 1 mg/day phylloquinone supplementation was given for 12 months. However, there was no significant difference in fasting blood glucose, insulin concentration, and HOMA-IR levels compared to the control group (16). In that study, although supplementation was performed for a longer period, it was not effective on insulin resistance, which is accepted as the initial stage of diabetes mellitus (16). In a recent meta-analysis, similarly, it was reported that Vitamin K supplementation does not affect insulin sensitivity (43). The lack of beneficial effects of these results on glucose metabolism as much as dietary intake suggests that the synthetic form of vitamin K may be ineffective.

It has been reported that studies supplementing animals may be useful in contradiction to human studies. Intraperitoneal undercarboxylated osteocalcin injection is known to affect glucose metabolism by increasing insulin secretion (44). In a study by Mizokami et al. (45), it was stated that GLP-1, one of the incretin hormones, increased the secretion of insulin by increasing intraperitoneal undercarboxylated osteocalcin injection in mice.

The Relationship Between Inflammation and Vitamin K

The role of Vitamin K in glucose metabolism is thought to be partly due to the modulation of diabetes-related cytokines and other metabolic risk markers (40). In addition, inflammation lies at the bottom of chronic metabolic diseases (46). Vitamin K causes a decrease in free radicals as a potential antioxidant (47). In vitro studies have shown that Vitamin K decreases the production of proinflammatory cytokines (40, 48, 49). Although it is not known how Vitamin K affects inflammation biomarkers, it is thought to suppress inflammation by decreasing the gene expression of cy-

tokines such as IL-6 (48). Additionally, it is known to have a protective effect against oxidative stress (50).

In a study on type-1 diabetic rats, Vitamin K1 treatment inhibited Nuclear Factor Kappa B (NF-KB) activation. This treatment is thought to possibly prevent beta-islet necrosis, favor beta-cell proliferation/regeneration, increase insulin production, and decrease hyperglycemia. Therefore, it is thought that Vitamin K1 supplementation may be beneficial for the complications of diabetes, not only for Type-1 diabetes, but also for beta-cell damage (41). It has been determined that the expression of genes involved in the acute inflammatory response is increased in Vitamin K deficient rats (48). Additionally, phylloquinone was found out to inhibit the activation of pro-inflammatory genes and prevent oxidative stress (41). In a study conducted on 1381 individuals, low plasma phylloquinone levels were associated with high pro-inflammatory markers (CRP and IL-6) (46).

In a study conducted on 379 healthy subjects, at three years follow up, it was determined that subjects with high cytokine concentration were associated with inadequate dietary Vitamin K (29). However, there was no significant difference in the concentration of cytokines such as IL-6 and CRP in individuals receiving phylloquinone supplementation (29). In a study conducted by Juanola-Falgarona et al. (40) on 510 people, the relationship between dietary Vitamin K intake and insulin-related peripheral adipokines and other metabolic risk markers related to Type-2 diabetes were investigated. It was determined that inflammatory cytokines such as leptin, tumor necrosis factor (TNF), interleukin (IL) -6 as well as other metabolic risk factors such as ghrelin, glucagon-like peptide-1, and visfatin were significantly decreased in the elderly who increased their phylloquinone intake for a year.

Reasons For Inconsistencies In The Studies

Human and animal osteocalcin genes differ from each other (33). The Vitamin K-associated osteocalcin gene is upregulated in humans with Vitamin D while it is downregulated in mice (33). Also, some amino acids and the levels of osteocalcin in mice and humans are different (27, 33). These differences seen in human and animal studies are attributed to serum osteocalcin level with age, growth, access to skeletal maturity and changes in day to day with menopause (51). In humans, non-carboxylated osteocalcin may occur as a result of decarboxylation during optimal Vitamin K uptake or osteoclast absorption (10). This situation may also cause contradictions. The food frequency qu-

estionnaires used in epidemiological studies were not sensitive enough to differentiate the phylloquinone and menaquinone intake. The reasons for the inconsistency of the results of the studies are thought to be the differences in the distribution and metabolism of menaquinone and phylloquinone in the body. In addition to sufficient positive effects of vitamin K taken as a supplement on people's glucose metabolism have not been observed.

CONCLUSION

The role of Vitamin K and osteocalcin on glucose metabolism and its possible mechanisms of action have been discussed in this review. Although the mechanism of action is not clearly understood, Vitamin K has been shown to reduce the risk of insulin resistance. It is thought that especially the menaquinone form prevents Type-2 diabetes. Despite the fact that there are many in vivo studies performed in mice, further human studies are required on this subject.

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RETRACTIONS & ERRATA

Date: 2020, June

Errata

In the article by Göztepe et al., entitled "Arrow Cause of Angina Pectoris: Single Coronary Artery in Elderly Patient" that was published in the February 2020 issue of Turkish Medical Student Journal, the name of the article was wrongly written. The Editorial Board reviewed the case and "Arrow Cause of Angina Pectoris: Single Coronary Artery in Elderly Patient" is corrected as "A Case Report: Single Coronary Artery in Elderly Patient".

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1.   I have read, and understood the Participant Information Sheet dated _____

2.   I freely agree to the use of my medical records for the purpose of this study.

3.   I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.

4.   I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant_____

Signature of Participant_____   Date _____

☐   The participant was informed through phone call and a verbal consent was obtained.

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure.

Name of witness (if appropriate)_____

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