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From the Editor

Dear readers,

In the first issue of 2023, we have prepared 11 research articles, a case report and two reviews that we think will be interesting for you. We hope that these articles will be a guide for healthcare professionals, especially primary care physicians.

Sorrow swept the world when the earthquake disaster struck Turkey on February 6, 2023, and deep physical and moral wounds were inflicted on our country. On behalf of the Ankara Medical Journal team, I would like to express our deep regret. I sincerely hope that such disasters will not be repeated, and I would like to express that we are determined to work harder so that our wounds are healed, and we can quickly return to our normal life.

We are proud that our journal has the highest citation rate among the primary care journals published in Turkey. Thank you for your growing interest in our journal.

Please stay tuned for the next issue.

Assoc. Prof. Dr. Ahmet Keskin

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Research Article

Ankara Med J, 2023;(1):1-12 // 10.5505/amj.2023.09609

DOCTORS' ATTITUDES AND PRACTISES REGARDING HUMAN PAPILLOMAVIRUS VACCINATION: A QUALITATIVE STUDY

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Abstract

Objectives: Human papillomavirus (HPV) is one of the most common sexually transmitted viruses in the world that causes diseases of the genitourinary system. But it is still not included in the national immunization schedule. Our aim is to find out the attitudes and practices of physicians in Türkiye regarding HPV vaccination.

Materials and Methods: The study was qualitative in nature. It was conducted with 14 subjects consisting of specialists in general medicine, family medicine, gynecology and obstetrics, urology, pediatrics and diseases working in Türkiye. A thematic framework analysis was used for the analysis.

Results: No notable difference was found in the opinions of the doctors in relation to their age or gender. The analysis revealed three main themes: Prejudice and ignorance about the HPV vaccine, insufficient information to patients about the HPV vaccine, and the need to include the HPV vaccine in the national immunization schedule.

Conclusion: The HPV vaccine is currently a paid vaccine, administered only on demand. Participants cited a lack of knowledge about the vaccine and the cost of the vaccine as the biggest barriers to vaccination. However, it is a vaccine that is considered necessary to be included in the "National Immunization Schedule".

Keywords: HPV vaccine, HPV infection, qualitative research.

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted viruses worldwide, causing diseases of the genitourinary system.[1] High-risk HPV types can cause primarily cervical cancer but also oropharyngeal, vulvar, vaginal, anal, and penile cancers.[2] Cervical cancer ranks fifth worldwide in terms of prevalence and fourth in women. It ranks third in cancer-related deaths among women, after breast and lung cancer.[3] Cervical cancer is one of the cancers that can be completely cured if diagnosed and treated early.[4] By the end of 2017, the HPV vaccine had been introduced in 80 countries.[5] The World Health Organization recommends HPV vaccination for adolescent girls between the ages of nine and thirteen and regular cervical cancer screening for women over the age of 30.[6] In Türkiye, cervical cancer is part of the routine screening program for women aged 30 to 65. As part of the screening, an HPV-DNA test and cervical smear test are performed every five years.[7] In preventive medicine, cervical cancer screening is one of the few screening methods that has been shown to reduce the incidence and mortality of invasive cancers.[8] However, vaccination protection is also very important in reducing the incidence of cervical cancer despite effective screening methods. HPV vaccination is recommended for adolescents and young adults in many countries. Studies have reported that the incidence of HPV infection and HPV-related disease decreased after HPV vaccination was initiated.[9]

During the literature review, it was found that attitudes toward cervical cancer and HPV vaccination vary from society to society.[10-14] Currently, two types of vaccines against HPV infection are being produced, which are also available in our country but haven't yet been included in the vaccination program by the Ministry of Health. The opinion of physicians is important at the stage of inclusion in the vaccination program. Therefore, we wanted to know their point of view. Our goal is to raise awareness about HPV vaccination and cervical cancer by learning about the attitudes and practices of physicians in our country about the HPV vaccine.

Materials and Methods

The study was conducted with specialists in general medicine, family medicine, gynecology and obstetrics, urology, pediatrics, and diseases practicing in Türkiye. The relevant specialists were reached through physician groups on social media. A preliminary questionnaire was sent online (**Box 1**), and the selected individuals who agreed to participate in the study were enrolled in the qualitative study.

Interviews were conducted from January 2021 to March 2021. Research participants were interviewed using semi-structured questions. The interview guide (**Box 2**) was based on similar studies in the literature, although it was adapted for each context. The "quota sampling" method was used for data collection. Because of the COVID-19 pandemic, interviews were conducted by telephone. Consent was again obtained from the participants during the telephone calls. The interviews lasted approximately 15-20 minutes. During the

interviews, the telephone speaker was turned on, and the audio was recorded with a recorder; the interviews were then transcribed. The collection of additional data was stopped after 14 interviews when we felt that no more additional information could be obtained. The transcriptions of the interviews were read and analyzed separately by two researchers. A thematic framework analysis was used to analyze the data. We began the analysis of the interviews by marking the themes that the participant highlighted in the interview texts, and a list of open coding was created. Following the coding, subcategories and main categories were formed. Finally, with the common aspects of the main categories, "main themes" are established as a grouping.

The categories that emerged from the researchers' analyzes were compared, and themes were extracted from the common categories.

Box 1. Pre-questionnaire form

Age:

Gender: Female ◯ Male ◯

Branch: Family Medicine ◯ Gynecology and Obstetrics ◯ General Practitioner ◯ Pediatrics ◯ Urology ◯

Duration in the profession: 1-5 years ◯ 5-10 years ◯ 10-15 years ◯ 15 years and over ◯

I would like to participate in the study by being interviewed on the subject.

YES ◯ **NO** ◯

Box 2. Interview guideline

- What do you think about the HPV vaccine?
- Do you recommend the vaccine to your patients?
- What feedback do you get from your patients when you recommend the vaccine?
- Do you recommend cervical cancer screening to your patients?
- Have you, your spouse or your children had the HPV vaccine? Do you think to have it done?
- What should be the place of the HPV vaccine in the vaccination schedule?

Results

Fourteen physicians (nine women and five men) were included in the study. Seventeen of them were from family health centers, and nine were from hospitals. Their mean age was 37 years. The characteristics of the physicians are shown in Table 1. Two of the physicians were general practitioners and worked as family physicians. The number of specialists in general medicine, pediatrics, urology, and gynecology and obstetrics was three. The median number of physicians had been in their profession for 14 years by the time of the interview.

After qualitative analysis of the interviews, no notable difference in physicians' opinions was found in relation to their age or gender.

Three main themes emerged from the analysis: Prejudice and ignorance about the HPV vaccine, inadequately informed patients about the HPV vaccine, and the need to include the HPV vaccine in the national vaccination schedule.

Table 1. Sociodemographic Characteristics of Physicians

Participant number	Age	Gender	Specialty	Duration in profession	Number of children	Affiliation
1	36	F	Pediatrics	10 years	No	University Hospital
2	41	M	Urology	16 years	2	Training and Research Hospital
3	37	M	Family Medicine	13 years	2	University Hospital
4	40	F	Gynecology & Obstetrics	16 years	2	State Hospital
5	35	M	Urology	10 years	0	State Hospital
6	30	F	Family Medicine	6 years	0	University Hospital
7	36	F	General Practitioner	12 years	1	Family Health Center
8	37	F	Pediatrics	13 years	2	Training and Research Hospital
9	38	F	Gynecology & Obstetrics	14 years	2	University Hospital
10	39	M	Urology	14 years	1	State Hospital
11	30	F	Pediatrics	6 years	0	Training and Research Hospital
12	31	F	Family Medicine	5 years	0	Family Health Center
13	54	F	Gynecology & Obstetrics	30 years	2	State Hospital
14	61	M	General Practitioner	32 years	2	Family Health Center

(F: Female, M: Male)

Prejudice and ignorance about the HPV vaccine

It turns out that many of the reasons for the prejudice against the HPV vaccine also apply to the other vaccines. The doctors who participated in our study stated that patients expressed fear of the side effects, reservations about the vaccine and fear of its effectiveness. It was found that those people who believe their knowledge to be true and are closed to other thoughts do not want to be vaccinated. *".....Those who do not want to get vaccinated are mostly those who think negatively about the vaccine and have a slightly more aggressive...mindset. I mean, there's this "I know better" thing! That's where it comes from."(N1)* Most participants stated that the vaccine is expensive and, therefore, they cannot get it. Most of those who wanted to get vaccinated gave up because of this. *"...The reasons why they do not get vaccinated are generally financial. Because the village where I work has a low socio-economic level... they get their children vaccinated for money, but not for HPV" (N3).*

It was also said that patients do not ask for the vaccine because it is a sexually transmitted disease, and the possibility of transmission increases with multiple partners. In addition, participating doctors said that patients do not ask for it because they live in a closed society.

One urologist who has been practicing for 14 years expressed this problem as follows. *"...It is not easy to tell parents to get their unmarried children vaccinated before their sexuality begins...because in our society it is generally accepted that sexuality begins with marriage."(N10)* The fact that people do not care about HPV and it is not as well known as other sexually transmitted diseases such as hepatitis, and AIDS was mentioned as another problem before vaccination. One of our participants, a urologist, explained that he recommends HPV vaccination, especially to young men who come to him with complaints of urethritis and discharge, to protect themselves and their partners, but this remains up in the air. *".....Hepatitis and AIDS are what they fear the most. They do not know much about HPV. When we say it, they cannot get serious because they do not know much about it. They already feel it. The conversation about HPV does not come to a conclusion. I say that the HPV they may get can cause cancer in their spouses even if they do not get cancer themselves. They get a little serious, but the conversation does not go any further than that."(N2).*

Inadequately informed patients about the HPV vaccine

HPV vaccination is usually recommended to patients and sometimes, the information about the vaccine cannot be conveyed due to lack of time or environmental conditions.

A participating pediatrician who works in a hospital that also serves immigrants expressed this situation as follows.
"...Those who ask for the vaccination usually ask with the intention of having it done, but it is very effective when

we ask them out of the blue, and because we have many Syrian groups, we cannot recommend it. We usually tell the parents of the young people..."(N8).

Another doctor commented as follows,

"...I do not recommend it at all. It is something that is not in my area of expertise as I am a pediatric urologist... Apart from that, I cannot rely on the socio-cultural level of the patients... " (N10)
In our study, some of the respondents felt that there was inadequate information about HPV from both doctors and the public.

".....I do not think other citizens, including doctors, have much information on this topic ..." (N7).

Some doctors indicated that primary care has more roles in providing information about HPV vaccination and cervical cancer screening.

One participant, who is a gynecologist and obstetrician, commented as follows. *"...Maybe this should be suggested more in primary care. Because in younger people or people whose sex life has not started yet, it is more effective ....(N9).*

The need to include the HPV vaccine in the national vaccination schedule

All the doctors who participated in our study were in favor of the vaccine and said that the vaccine should be included in the national vaccination schedule. Most of the doctors interviewed felt that the vaccine should be given to both boys and girls, but primarily to girls.

"...It should be given to both if it is possible, but primarily to girls..." (N3).

A urologist who has been practicing medicine for 10 years stated that women should be vaccinated because there are not as many complications in men. Another urologist with 14 years of medical experience expressed a similar opinion,

"...The harm of the disease is greater in women. I think that should be the primary goal for women. It's a big goal to do it for both men and women. That means sharing the effort. I think women should come first..." (N2).
A 30-year-old pediatrician stressed that there are other vaccines that should be included in the national immunization schedule.

"...There are other vaccines that take precedence. For example, meningococcal. But of course, this vaccine should also be....."(N11).

Discussion

The HPV vaccine is an optional, paid-for vaccine that is not included in the national immunization schedule. This qualitative study shows that physicians believe the HPV vaccine is necessary. However, the major barriers to vaccination include the high cost of the HPV vaccine, negligence and lack of information about the vaccine.

Strengths and limitations

This study is the first qualitative evaluation of the HPV vaccine in Türkiye from the perspective of medical professionals. The HPV vaccine is not included in the "National Vaccination Schedule" and it is assumed that it will be included in the vaccination schedule. But this is still not certain. So we expect to fill the knowledge gap from the doctors' point of view. This study also has certain limitations. First of all, the number of doctors we included (n = 14) may be too small. However, we stopped including additional interviews when we felt we had reached saturation, and no further information could be obtained from additional interviews. We reached physicians in the specialties of family medicine, urology, pediatrics and gynecology and obstetrics, who mostly see patients with HPV infections and are more likely to provide information about HPV vaccination. Finally, our results cannot be generalized to all doctors, but the data obtained give a good picture of doctors' current thinking.

Comparison with existing literature

Undoubtedly, physicians' knowledge, attitudes and behaviors regarding vaccination are crucial to protect public health. Therefore, the fact that the doctors in our study think that the HPV vaccine is necessary is very important.

HPV vaccination is recommended for adolescents and young adults in many countries. The studies reported that the incidence of HPV infections and HPV-related diseases decreased after HPV vaccination was started.[9] In our country, the quadrivalent vaccine (effective against HPV 6-11-16-18) was licensed in 2007 and the bivalent vaccine (effective against HPV 16-18) in 2008.

Physicians who are involved in women's health issues or work with patients who are at high risk for HPV-related diseases may have a better understanding of HPV infections and can therefore recognize the potential health benefits of HPV vaccination. One study has also shown that experience with adolescents is related to willingness to recommend vaccines against sexually transmitted infections (STIs).[15] The clinicians in our study also worked with high-risk patients.

The literature search revealed that the specialties in which the relevant studies were conducted mostly consisted of family medicine, pediatrics and gynecology and obstetrics. However, the studies conducted were quantitative studies and no qualitative studies were found. In a study conducted with pediatric specialists in Türkiye, 91.1% of the 438 physicians who participated in the study recommended the administration of the HPV vaccine.[16]

In a study whose population consisted of a random sample of 1,000 physician members of the American Academy of Family Physicians (AAFP), participants considered the HPV vaccine more important than, or as important as vaccines against the following diseases: Anthrax (78%/12%), genital herpes (42%/51%), chlamydia (39%/52%), tuberculosis (28%/42%), influenza (22%/46%) and hepatitis B (14%/59%). Eight of the 10 most frequently cited barriers were related to parental barriers to vaccination.[17] In our study, one doctor stated that the meningococcal vaccine, which is not included in the "National Immunization Schedule", has priority over HPV.

Although the potential harm of HPV is higher in women, it can lead to complications in both sexes. Although most doctors in our study believe that vaccination is appropriate in both sexes, they believe that it should be given primarily to girls. This situation is consistent with the literature.[16-17]

When studies conducted with parents in the literature were examined, they also showed that parents tend to have their daughters vaccinated predominantly against HPV.[18] In contrast, Seven et al. found that parents in Türkiye are more willing to vaccinate their sons than their daughters.[19] The literature reports that many families have limited knowledge about HPV infection and the HPV vaccine, but acceptance of the vaccine increases when their physicians recommend it.[20-21] In a survey of gynecologists, Raley et al. also found that beliefs about the HPV vaccine's properties, such as efficacy, were important predictors of physician recommendation.[22] In our study, physicians also emphasized that people are not adequately informed about the HPV vaccine.

In Bouchez's qualitative study, physicians reported three different ways of interacting with patients: informing and persuading, conforming to patient opinion, and refusing to compromise on vaccination.[23] In a systematic literature review of factors influencing hesitation to HPV vaccination in Europe, participants most frequently cited problems with the quantity and quality of available information about HPV vaccination, followed by concerns about possible side effects of the vaccine and distrust of health authorities, medical personnel and new vaccines.[24]

One of the barriers to vaccination is that the vaccine comes at a cost. In a study conducted in Türkiye, the rate of agreement with the sentence "If the HPV vaccine is covered by social security, then I will get vaccinated" was 51.8%.25 In another study, 93% of participants found the HPV vaccine expensive, even though they got

vaccinated.[9] In a systematic review of parents' knowledge, beliefs, acceptance and uptake of the HPV vaccine in Association of Southeast Asian Nations (ASEAN) member countries, uptake was high when the vaccine was offered free of charge.[26]

The financial situation significantly influences people's decisions in the area of health, as in any other area. In general, people do not hesitate to spend money on health if they understand its importance very well. Therefore, the importance of HPV vaccination should be explained in more detail until it is included in the vaccination schedule, and the public should be made aware of this issue. Among the caveats in the literature, the proportion of families who have concerns that vaccination may encourage risky sexual behavior varies between 30-60%.[27-29] In our study, doctors did not mention such a caveat. Some doctors simply said that some people are afraid to talk about sexual issues and are, therefore, reluctant to ask about this vaccine. Even if some parents have reservations about vaccination against sexually transmitted infections, doctors can be reassured because many parents find vaccination against sexually transmitted infections (STIs) acceptable.[15,30]

In the study conducted by Raley et al., the American University of Obstetricians and Gynecologists (ACOG) recommendations on this aspect were shown to have the greatest influence on gynecologists when recommending HPV vaccination to their patients.[22]

The issuance of similar statements by the Turkish Pediatricians Association, the Turkish Family Medicine Specialists Association and the Turkish Urologists Association will have a positive impact on awareness of HPV vaccination.

Although the HPV vaccine is to be included in the "National Immunization Schedule", the vaccine is currently a paid vaccine that is administered only on demand. For this reason, doctors' recommendation of the vaccine will increase confidence in the vaccine and reduce HPV complications, at least among those who can afford the vaccine. However, reducing HPV-related mortality across society depends on completing vaccination before sexual activity begins.

Ethical Considerations: Ethical approval was acquired from the local Ethics Committee (22/07/2020-08).

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Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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EVALUATION OF PROGNOSIS, MORTALITY AND PLATELET INDEXES, PLATELET/LYMPHOCYTE AND NEUTROPHIL/LYMPHOCYTE RATIOS OF PALLIATIVE CARE PATIENTS

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Abstract

Objectives: In this study, it was aimed to evaluate the clinical significance of platelet indices, platelet, neutrophil, and lymphocyte values, as well as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) values and their relationship with mortality in palliative care patients.

Materials and Methods: The data of 464 patients in the palliative care service were analyzed retrospectively. Sociodemographic characteristics of the patients, diagnosis, length of stay in the service, the way they were admitted to the palliative service and the way they were discharged from the palliative service, hospitalization and hematological parameters were recorded.

Results: The mean age of the 464 patients included in the study was 75.15±13.63 years. It was seen that 68.30% of the patients were alive during the time period they were included in the study. When the admission and discharge blood values of the patients who died and the patients who survived were compared, the WBC and neutrophil values of the patients who died were found to be higher than the patients who survived, while the platelet and lymphocyte values of the patients who died were found to be lower. While admission and discharge NLR values, admission PLR values, discharge MPV values and discharge PDW values were found to be significantly higher in patients who died than in patients who survived, discharge PCT value was found low.

Conclusion: Leukocytosis, thrombocytopenia, lymphopenia, and neutrophilia were dominant in the hematological parameters of the patients who died compared to the patients who survived. In contrast, the admission PLR value was found to be higher in patients who died than the patients who survived.

Keywords: Palliative care, prognosis, mortality.

Introduction

Palliative care is a multidisciplinary approach that aims to achieve a good quality of life by preventing or alleviating the physical, psychosocial, and spiritual distress of patients who face problems caused by life-threatening diseases through early detection and comprehensive evaluation.[1] Today, it is known that patients with neurological diseases and advanced cancer need palliative care with a well-coordinated team to determine their needs and provide effective care.[2]

Neutrophilia, lymphopenia, and thrombocytopenia in peripheral blood are evaluated as responses to systemic inflammation.[3,4] In recent years, the relationship of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and mean platelet volume (MPV) obtained from routine complete blood count with various diseases and their effects on mortality in critically ill patients especially cancer patients, have been investigated and valuable results have been obtained.[5-8] In a study investigating the prognostic importance of platelet indices performed in a mixed intensive care unit, it was concluded that MPV and platelet distribution width (PDW) values were positively correlated with disease severity and negatively correlated with platelet count and that PDW and PCT values were prognostic biomarkers defining disease severity, such as platelet level.[3] Senyurt et al.[9], in their study on patients hospitalized in an intensive care Unit, found a significant difference in hemogram parameters (MPV, RDW, NLR, PLO) between deceased patients and survivors. They observed that the discriminating power of the hemogram parameters for mortality was higher than SOFA (Sequential Organ Failure Assessment), APACHE II (Acute Physiology and Chronic Health Evaluation) scores, and CRP (C-Reactive Protein). These parameters can be obtained or calculated automatically with complete blood count devices at low cost and have advantages such as rapid decision-making in critically ill patients and initiation of appropriate treatment.

In our study, it was aimed to evaluate the clinical importance of routinely studied platelet indices (PCT, MPV, PDW), platelet, neutrophil, and lymphocyte values, as well as easily calculated NLR and PLR values, and their relationship with mortality in palliative care patients who are exposed to many factors that may affect hematological parameters.

Materials and Methods

This study was designed as a retrospective, cross-sectional and analytical study. It was conducted with the data obtained by retrospectively scanning a total of 495 patients who were hospitalized in the Palliative Care Service of the local University Training and Research Hospital. The examinations and information to be used in the study were obtained from the records of the hospital. If the same patient had more than one admission during

this period, the first hospitalization data were included in the study. Thirty-one of 495 patients were excluded from the study due to missing data, and the data of 464 patients were evaluated in the study.

The data of the patients were evaluated retrospectively. Sociodemographic characteristics such as age, gender and marital status of the patients, diagnosis/pre-diagnosis, length of stay in the service, the way of being admitted to the palliative service (emergency, outpatient clinic, intensive care, other services) and the way of discharge from the palliative service (intensive care transfer/referral, Transfer/transfer to other services, discharged with recovery, death), hospitalization and discharge hematological parameters were studied and recorded. Hematological parameters such as thrombocyte indices (MPV, PDW, PCT), leukocytes, lymphocytes, neutrophils, thrombocytes, NLR and PLR values were recorded.

Statistical Analyses

The obtained data were analyzed with SPSS (Statistical Package for the Social Sciences) 21 package program. The numerical data were evaluated using descriptive statistics (number, percentage, mean, standard deviation). Mann-Whitney U test was used for comparisons between groups when the data were not normally distributed. Chi-Square analysis and Correlation analysis were used for the relationship and/or dependency between the variables. It was stated if there was a significant difference if the level of significance was $p<0.05$.

Results

In our study, 464 patients admitted to the Palliative Service of the local University Training and Research Hospital were included. In the study, 58.84% of the patients were male, 52.62% were married, and the mean age was 75.15 ± 13.63 years. The mean length of stay in the hospital of the patients in the palliative service was 22.62 ± 23.51 days.

The patients in our study had at least one chronic disease. In the study, 70.32% of them had hypertension, 68.52% neurological diseases and 50.61% cardiovascular diseases. Oral intake disorder was present in 56.32% of the patients, and pressure ulcer was present in 42.53% of the patients. In the study, 41.82% of the patients were sent from family medicine outpatient clinics and other outpatient clinics. When the discharge status from the service was examined, it was found that 59.91% of them were discharged with recovery. It was found that 57 (90.50%) of 63 patients transferred to the intensive care unit died during intensive care therapy. It was observed that 68.30% of the 464 patients were alive, and 31.70% died in the period they were included in the study (Table 1).

Table 1. Sociodemographic, clinical characteristics, hospitalization, and mortality rates of the patients

Variables	n	%
Gender		
Female	191	41.16
Male	273	58.84
Marital status		
Single	29	6.32
Married	244	52.62
Not mentioned	191	41.16
Chronic diseases		
Diabetes mellitus	128	27.61
Hypertension	326	70.32
Cardiovascular disease	235	50.61
Neurological disease	318	68.52
Malignancy	134	28.91
Pulmonary disease	232	50.00
Pressure ulcer	197	42.53
Oral feeding disorder	261	56.32
Units that referred patients to the palliative service		
Family medicine clinic	194	41.82
Emergency clinic	129	27.82
Intensive care unit	100	21.63
Other services	41	8.82
Discharge from palliative care		
Discharge with recovery	278	59.91
Transfer to an intensive care unit	63	13.62
Transfer to other services	33	7.13
Death	90	19.42
Survival status of patients who were sent to an intensive care unit		
Died	57	90.50
Survived	6	9.50
Total	63	100
Mortality status		
Survived	317	68.30
Died	147	31.70
Total	464	100

(n: number)

There was a statistically significant no difference between the patients' mortality status and age (p=0.495), length of stay in the service (p=0.319), gender (p=0.054), and marital status (p=). 0.349, and the unit that admitted to palliative service (p=0.086). The mortality rate was numerically higher in males (35.24%), aged 51-60 (42.92%), married (34.43%), and patients sent from the emergency department (39.51%).

In our study, the mortality rate of patients with malignancy and without neurological disease was found to be statistically significantly higher (p<0.001) (Table 2).

Table 2. Comparison of Mortality Status of Patients According to Concomitant Diseases

Concomitant Diseases		Survived		Died		Total	p
		n	%	n	%	n	
Diabetes Mellitus	No	229	68.18	107	31.82	336	0.902
	Yes	88	68.82	40	31.18	128	
Hypertension	No	92	66.71	46	33.29	138	0.619
	Yes	225	69.09	101	31.01	326	
Cardiovascular disease	No	159	69.39	70	30.61	229	0.611
	Yes	158	67.28	77	32.72	235	
Neurological disease	No	75	51.44	71	48.56	146	**<0.001**
	Yes	242	76.17	76	23.83	318	
Malignancy	No	257	77.91	73	22.09	330	**<0.001**
	Yes	60	44.82	74	55.18	134	
Pulmonary disease	No	153	65.88	79	34.12	232	0.272
	Yes	164	70.73	68	29.27	232	
Total		317	68.30	147	31.70	464	

In our study, the hematological parameters of the patients in the first blood tests taken at the time of admission to the hospital were recorded as the first results, and the hematological parameters in the last blood tests before discharge from the service (death, discharge, transfer) were recorded as the second results. There was no significant difference between the age and gender of the patients in terms of hospitalization and hematological parameters at discharge.

The comparison of the first and second hematological parameters (PLR, NLR, MPV) of the patients according to the comorbid conditions is given in Table 3.

Accordingly, the mean values of 1. PLR, 1. NLR, and 2. NLR were found to be statistically significantly lower in patients with diabetes mellitus than in patients without diabetes mellitus. The mean values of 1. PLR, 1. NLR, and 2. NLR were statistically significantly lower and 1. MPV mean values were higher in neurological patients compared to those without. The mean values of 1. PLR, 2. PLR, 1. NLR and 2. NLR were statistically higher and 1. MPV mean values were lower in patients with malignancy compared to those without. The mean values of 1. PLR, 1. NLR, 2. NLR were statistically significantly lower and 2. MPV mean values were higher in patients with pressure ulcers compared to those without. (Table 3). When admission and discharge hematological parameters of the patients were compared, it was seen that the 1. PLR value was statistically significantly higher than the 2. PLR value. There was no significant difference between admission and discharge results in other parameters.

When hospitalization and discharge, hematological parameters were compared according to the survival status of the patients, the mean values of the 2. WBC, 2. Neutrophil, 2. Lymphocyte, 2. MPV, 1. PLR, 2. NLR, 2. MPV, and

2. PDW of the deceased patients was found to be significantly higher and 2. Platelet and 2. PCT values were found to be significantly lower compared to the patients who survived (Table 4).

Table 3. Comparison of Patients' Diseases and PLR, NLR, MPV Values

Variables		DM	HT-CRD	KVD	ND	Malignancy	PD	Pressure ulcer
1. PLR	No	268.83 ± 209.78	256.14 ± 223.46	262.75 ± 206.46	289.72 ± 233.61	232.24 ± 154.01	253.52 ± 208.88	270.43 ± 204.47
	Yes	221.26 ± 151.38	255.52 ± 184.15	248.85 ± 186.30	240.09 ± 174.95	313.51 ± 266.26	257.89 ± 183.53	235.74 ± 183.58
	P	**0.014**	0.575	0.383	**0.034**	**0.002**	0.372	**0.021**
2. PLR	No	250.31 ± 219.07	250.10 ± 227.05	261.29 ± 235.67	284.47 ± 288.29	217.85 ± 161.95	245.61 ± 239.75	269.81 ± 247.67
	Yes	235.76 ± 212.89	244.68 ± 213.31	231.69 ± 197.09	228.77 ± 173.04	316.34 ± 304.11	246.98 ± 192.67	214.43 ± 162.71
	P	0.126	0.872	0.268	0.651	**0.039**	0.093	0.052
1. NLR	No	9.43 ± 11.65	8.72 ± 10.54	9.05 ± 9.97	10.56 ± 10.81	7.42 ± 7.87	8.82 ± 10.19	9.47 ± 10.47
	Yes	7.51 ± 8.13	8.98 ± 10.95	8.76 ± 11.60	8.14 ± 10.75	12.56 ± 15.33	8.98 ± 11.43	8.13 ± 11.25
	P	**0.022**	0.473	0.241	**<0.001**	**<0.001**	0.582	**0.006**
2. NLR	No	14.70 ± 76.85	9.68 ± 11.13	12.20 ± 19.20	22.70 ± 115.52	12.57 ± 77.64	10.51 ± 16.54	17.51 ± 86.52
	Yes	9.75 ± 18.25	14.88 ± 78.52	14.43 ± 91.02	9.03 ± 14.79	15.20 ± 17.21	16.16 ± 92.03	7.67 ± 10.35
	P	**0.038**	0.583	0.084	**<0.001**	**<0.001**	0.646	**<0.001**
1. MPV	No	10.01 ± 1.42	9.82 ± 1.31	9.93 ± 1.52	9.81 ± 1.44	10.02 ± 1.41	10.04 ± 1.54	10.03 ± 1.52
	Yes	10.02 ± 1.52	10.02 ± 1.51	10.03 ± 1.43	10.02 ± 1.44	9.81 ± 1.44	9.92 ± 1.32	9.93 ± 1.31
	P	0.668	0.061	0.281	**0.048**	**0.017**	0.209	0.408
2. MPV	No	10.29 ± 4.94	10.48 ± 7.50	9.93 ± 1.49	10.00 ± 1.62	10.29 ± 4.95	10.13 ± 1.42	10.22 ± 1.50
	Yes	10.09 ± 1.52	10.14 ± 1.51	10.53 ± 5.82	10.34 ± 5.05	10.10 ± 1.72	10.34 ± 5.88	10.27 ± 6.34
	P	0.948	0.149	0.219	0.802	0.665	0.183	**0.037**

(P, Mann-Whitney U test; DM, Diabetes Mellitus; HT-CRD, Hypertension-chronic kidney disease; CVD, Cardiovascular diseases; ND, Neurological diseases; PD, Lung Diseases.)

Table 4. Comparison of Hospitalization and Discharge Hematological Parameters According to the Survival Status of the Patients

Variables	All Patents (464)	Survived (317)	Died (147)	P**
1. WBC	10.48±5.94	10.20±5.69	11.06±6.44	0.258
2. WBC	10.87±6.77	9.26±5.31	14.34±8.16	**<0.001**
P*	0.948	**0.003**	**<0.001**	
1. Platelet	266.02±124.11	272.33±119.22	252.52±133.43	0.051
2. Platelet	259.11±134.43	277.01±129.34	220.53±137.41	**<0.001**
P*	0.139	0.414	**0.002**	
1. Neutrophil	8.16±5.13	7.74±4.52	9.07±6.18	**0.035**
2. Neutrophil	8.44±6.14	6.69±4.52	12.23±7.37	**<0.001**
P*	0.711	**<0.001**	**<0.001**	
1. lymphocyte	1.52±2.73	1.67±3.22	1.20±.99	**<0.001**
2. lymphocyte	1.54±1.43	1.56±.91	1.50±2.18	**<0.001**
P*	0.051	0.563	**0.045**	
1. PLR	255.71±196.42	235.13±156.61	300.08±257.60	**0.017**
2. PLR	246.29±217.26	229.56±185.16	282.37±271.22	0.476
P*	**0.031**	0.430	0.479	
1. NLR	8.90±10.82	7.52±8.13	11.88±14.67	**<0.001**
2. NLR	13.33±66.10	7.58±13.42	25.74±115.07	**<0.001**
P*	0.494	0.941	0.149	
1. MPV	10.01±1.43	9.92±1.41	10.14±1.53	0.288
2. MPV	10.24±4.28	10.10±5.03	10.54±1.78	**<0.001**
P*	0.168	0.536	**<0.001**	
1. PDW	15.14±2.32	15.02±2.23	15.13±2.41	0.188
2. PDW	15.47±7.64	14.99±2.27	16.52±13.13	**<0.001**
P*	0.299	0.724	0.194	
1. PCT	0.26±0.12	0.26±0.13	0.24±0.12	0.069
2. PCT	0.25±0.11	0.26±0.10	0.22±0.13	**<0.001**
P*	0.102	0.551	**0.017**	

(*:t-test; **: Mann-Whitney U test)

Discussion

Our study aimed to evaluate the thrombocyte indices, PLR and NLR values, mortality, and prognosis by examining the blood tests of the patients hospitalized in the palliative care service.

Malignancy and neurological diseases were more prominent as the primary diagnosis in patients in the palliative service. It is seen that 68.30% of the 464 patients were alive and 31.70% died during the study period. While the mortality was high in the presence of malignancy, it was lower in those with neurological disease. Since patients with malignancy have generally completed their treatment and are referred to the palliative care service in the terminal period, high mortality in these patients is a possible outcome.[10] Patients with neurological diseases have problems such as nutritional problems, pressure ulcers, muscle tone disorder, and

infection, and therefore they need more care. [11] In a similar study conducted by Yuruyen et al.[10], it was found that 52.1% of the patients in the palliative care service were discharged with recovery, 15.3% were referred, and 33.6% died. In our study, it was observed that the mortality (39.5%) of the patients in the palliative service transferred from the emergency room was numerically higher. This may be related to the fact that the patients taken over from the intensive care unit no longer need intensive care, and their general condition is relatively stable. It may also be related to the fact that the reasons for admission of patients referred from the emergency department are acute and serious problems.

Platelet indices obtained by complete blood count (MPW, PDW, PCT), PLR and NLR have recently been considered valuable in terms of their use as inflammatory markers.[5,6] It attracts attention in terms of being affordable and easily accessible. At the same time, there are many studies that may be prognostic and mortality markers for various diseases.[7,8] In our study, the patients had at least one chronic disease. NLR, PLR and exit NLR levels in the admission of patients with diabetes (27.61%) were found to be lower than those without diabetes. In a study by Sayıner et al.[12] in which they studied the relationship between NLR levels and microvascular complications of diabetes, NLR levels were found to be high in diabetic patients, and researchers attributed this increase to subclinical inflammation occurring in microvascular complications and reported that it is a cost-effective marker in demonstrating microvascular complications. Mertoglu et al. [13] investigated whether NLR, PLR and MPV levels could be predictive markers in prediabetic and diabetic patients. The fact that the changes in NLR levels in diabetic patients in our study were different from other studies may be due to the presence of many other concomitant diseases and conditions in the patients at the same time.

It is argued that the physiological response of leukocytes in the systemic circulation to stress with the effect of granulocyte colony-stimulating factor, tumor necrosis factor-alpha, interleukin-1 and interleukin-6 in cancerous tissue causes an increase in neutrophil count and a decrease in lymphocytes.[14] It has been suggested that changes in NLR and PLR may be associated with tumor growth and metastasis, and this may play a prognostic role. IL-6 is an important cytokine that stimulates tumorigenesis. There is a study showing a positive relationship between MPV and IL-6 and thrombopoietin.[15] Özyalvaçlı et al., in their study on 120 patients with breast cancer and 50 patients with benign proliferative breast disease, reported that high preoperative NLR levels had a high predictive value in predicting malignant cases and NLR levels were a significant prognostic factor for breast cancer.[16] In a study by Kulaksızoğlu et al. in which 492 colorectal cancer patients and 327 control groups were included, NLR and PLR values were found to be significantly higher than in the control group, and it was stated that high NLR and PLR levels in colorectal cancer patients could be an important biomarker in determining the disease.[17] Similarly, there are studies showing that high PLR levels observed in malignancies such as ovarian, colorectal, esophageal, pancreatic, and endometrial cancer are associated with poor prognosis.[19-21] In our study, 134 (28.91%) patients with malignancy had higher NLR and PLR levels and lower MPV levels at admission compared to patients without malignancy.

In our study, admission NLR, PLR values and discharge NLR values of patients with neurological diseases were found to be lower, and admission MPV levels were found to be higher than that of patients without neurological disease. In the study of Bolayır et al., it was reported that NLR and PLR levels increased in patients with acute-stage intracerebral hemorrhage and that this elevation was closely associated with short-term mortality in patients with intracerebral hemorrhage.[21] In a study investigating whether NLR and MPV values can be used as predictive factors in stroke; While NLR levels were found to be higher in stroke patients than in healthy individuals, no association was found between MPV levels and stroke risk and stroke prognosis.[22]

In our study, admission NLR, PLR and discharge NLR levels were lower, and discharge MPV levels were higher in patients with pressure ulcers compared to that of patients without. Pressure ulcers are more common in the intensive care unit, geriatric, and neurology services.[23] This explains why the comparison of NLR, PLR and MPV levels of patients with pressure ulcers had similar results with patients with neurological disorders in our study.

In our study, admission and discharge values of patients who died or survived were compared to investigate the effect of hematological parameters on mortality. Discharge WBC values of patients who died were found to be higher than the admission WBC values of patients who survived. In the patients who survived, discharge WBC values were found to be lower than admission WBC levels. Leukocytosis occurs in many conditions, especially in infection, inflammation, myeloproliferative diseases, and stress.[24] Akbas et al.[25] reported that leukocytosis has a predictive value in mortality. Thrombocytopenia is also an independent risk factor that increases mortality in critically ill patients.[3] In the study of Coşkun et al., including 237 patients followed in the intensive care unit, thrombocytopenia was shown to be associated with high mortality.[26] In the study performed by Haksiyer et al. in the intensive care unit, the mortality rate was found to be higher in patients with thrombocytopenia, and it was reported that the most common causes of thrombocytopenia were sepsis and DIC.[27] In our study, discharge platelet levels of patients who died were lower than in admission values of the same patients and that of patients who survived. These results, similar to other studies, show that thrombocytopenia accompanies mortality.

Both neutrophilia and lymphopenia can be considered acute-phase reactants.[4] In a study comparing patients with small cell lung cancer and the healthy group, increased neutrophil and decreased lymphocyte levels were associated with decreased survival. [28] In our study, when the neutrophil and lymphocyte values of the patients who died and the patients who survived were compared, it was observed that the neutrophil levels were high, and the lymphocyte levels were low, similar to the literature. When the admission and discharge blood values of the patients were compared, the discharge neutrophil value was found to be low in the patients who survived, while the discharge neutrophil and lymphocyte values were found to be high in the patients who died.

Many studies have shown a direct correlation between mortality and higher rates of NLR and PLR in different patient populations. Kutlucan et al. [29] showed that high PLR and NLR levels might be an indicator for the development of nosocomial infections and may prolong hospital stays. In our study, both admission and discharge NLR levels and admission PLR levels were found to be significantly higher in the patients who died compared to the patients who were alive.

Patients in critical care services, such as palliative care services and intensive care units, often have many different comorbidities. Therefore, it is very difficult to determine the effect of a particular disease on platelet indices (MPV, PDW, PCT) in palliative care services and intensive care units.[3] In a study conducted to investigate the relationship between platelet indices and their performance in predicting disease severity and mortality, 261 critically ill patients were included; high MPV and PDW levels and low platelet and PCT levels have been associated with more severe disease and higher mortality compared to patients with normal platelet index.[30] Efe et al. investigated the prognostic importance of platelet indices in critically ill patients in the intensive care unit and found that MPV and PDW levels were correlated with each other.[3] It has also been reported that they show a positive correlation with the severity of the disease and a negative correlation with the platelet count. In our study, discharge MPV and PDW levels were found to be higher in patients who died compared to patients who survived, while discharge PCT levels were found to be lower.[3]

The limitations of our study are that our study is a retrospective and single-center study and that our parameters are not compared as multiple measurements but just as two measurements, the first blood test after admission to the service and the last blood test before discharge from the service. The best aspect of our study is that it is the first original study to examine the platelet indices, NLR and PLR values of palliative care service patients. In addition, it is one of the few studies evaluating critically ill patients who are under the influence of many factors affecting hematological parameters. However, further multicenter, prospective and cohort studies are needed.

In this study, a contribution was made to the literature by evaluating platelet indices, platelet, neutrophil, lymphocyte values, NLR and PLR values, and prognosis and mortality in palliative care patients.

Conclusion

In our study, 31.70% of the patients hospitalized in the palliative service died. Mortality rates were found to be numerically higher in patients transferred from the emergency department with malignancy and lower in patients with neurological disease. In the last blood tests of the patients who died, leukocytosis, thrombocytopenia, lymphopenia, and neutrophilia were more common than the patients who survived. The admission NLR, PLR and discharge NLR, WBC, neutrophil, lymphocyte, MPV, and PDW levels were found to be higher in the patients who died, and the discharge platelet and PCT levels were found to be lower in the patients

who survived. It was observed that the mean of admission PLR value was higher than the discharge value. The discharge WBC and neutrophil values of the patients who survived were found to be lower than the admission values.

Ethical Considerations: The study was carried out with the approval of the E-77192459-050.99-3000 dated 14.01.2021 and numbered 2021/423 of the Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine of the local University.

Conflict of Interest: The authors declare no conflict of interest.

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NUTRITIONAL STATUS OF HOME CARE PATIENTS AND AFFECTING FACTORS THROUGHOUT A SIX MONTHS FOLLOW-UP PERIOD

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Abstract

Objectives: Home care patients are highly susceptible to malnutrition. This study, it was aimed to determine the changes in nutritional status and the factors affecting this change in the patients who receive home care services.

Materials and Methods: This study was conducted as a prospective descriptive field study. Patients were visited twice with an interval of 6 months, and the MNA test was applied in both visits. The test scores and the factors affecting them were examined with Student's t-test, Pearson Chi-square and correlation tests considering the compatibility of the data with the normal distribution. Data were analyzed with IBM SPSS ver.22 statistical program.

Results: On the first visit, 38.13% of patients were malnourished, and 37.81 % were at risk of malnutrition, and at the second visit, 41.88% were malnourished, and 35.31% were at risk of malnutrition. A statistically significant relationship was found between the MNA classification and loss of appetite, economic problems, caregiver not providing nutritional support, lack of social security, polypharmacy, and inability to eat alone.

Conclusion: Screening the nutritional status of patients given home health care with appropriate scales and at short intervals, identifying those at risk of malnutrition and improving their nutritional status with appropriate interventions will positively affect the general health status and quality of life of these patients.

Keywords: Nutritional status, home care services, malnutrition, risk factors.

Introduction

Today, many factors, such as the extension of the average life expectancy, an increase in the elderly population in need of medical support, and developments in medicine and technology that allow many health services to be implemented at home, increase the importance of home health services.[1]

The home care patient group is more likely to have malnutrition due to advanced age and accompanying diseases such as dementia, depression, decreased oral intake, swallowing, and chewing problems, inability to eat alone, immobility, loss of appetite, nausea and vomiting. The problem of malnutrition has important effects on morbidity, mortality, disease complications, length of hospital stay, tolerance to treatment, prognosis, and quality of life, which affect the function and healing of all body systems.2 In epidemiological studies, globally, about 13–78% of older adults are suffering from malnutrition; this rate increases up to 90% in those hospitalized for acute illness, and this rate is 30-60% in nursing homes or long-term care recipients.[3,4,5] Among the factors that negatively affect nutritional status, the following factors take an important place: environmental factors such as physiological changes that occur with aging, acute and chronic diseases, dental and oral health problems, polypharmacy, economic problems, not being able to shop alone, not being able to prepare and eat food.

Studies have shown that approximately 75% of the elderly with malnutrition or at risk for malnutrition do not receive any treatment.[6] It is thought that the most important reason for this is that malnutrition that starts in the elderly goes mostly unnoticed. In elderliness, even if no other factors play a role, the mortality rate increases by 9-38% within 1-2,5 years from the beginning of weight loss alone.[7]

These data show the importance of regular screening of home care patients for malnutrition. To reduce mortality and morbidity and to increase the quality of life, early evaluation of home care patients, who are most likely to experience malnutrition, in terms of factors that negatively affect their nutritional status, and determination of their nutritional levels at periodic intervals are important and necessary.[8]

One of the most commonly used methods for screening for malnutrition is the MNA test. It has been reported that the use of the MNA test in the monitoring of malnutrition will be beneficial in measuring the effect of nutritional support.[9]

In light of this information, the aim of our study was to determine the changes in the MNA test and the factors affecting this change during the care period that the patients were receiving home care.

Materials and Methods

This research, which was planned as a prospective descriptive field study, was carried out after obtaining ethical approval. The universe of the study consisted of 1479 patients who applied to the Home Care Services of a tertiary hospital for the first time. Since a 5% margin of error and 95% confidence level were targeted in the study, it was calculated that at least 306 patients should be reached. Considering possible data losses, 10% was added to this number, and it was decided to reach a total of 340 patients. Patients who were visited at least two times with an interval of 6 months between November 2017 and September 2018 were included in the study. Since the study was carried out together with the service delivery, the sample was not selected, and all patients who agreed to participate were included in the study on a voluntary basis throughout the study period. In this way, a total of 342 patients were reached, nine patients were discharged as exitus during the study process, 11 patients did not want to continue working and two patients were excluded from follow-up due to a change of address. In this way, the study was completed with 320 patients.

In addition to the MNA test, the research data were collected using a sociodemographic data form prepared by the researchers in accordance with the current literature and a questionnaire questioning the factors affecting nutrition. Questionnaire forms were filled according to the answers received from the patient in cases where communication could be established and from the caregivers in cases where communication could not be established with the patient. All data were collected by the researcher by face-to-face interview method.

In the first section of the questionnaire prepared by the researchers, the patient's sociodemographic data, the patient's age, gender, primary diagnosis that caused him/her to be dependent on the home, the drugs he/she used, the closeness of the caregiver and the degree of dependence of the patient was questioned. In the second section of the questionnaire, 14 questions were asked to evaluate the factors affecting nutrition and they were asked to indicate their answers in a 5-point Likert format (1 least important / 5 most important). The questions in the survey included the following topics; low dietary intake, inability to prepare food, loss of appetite, economic problems, failure of caregivers to provide nutritional support, low functional status, not having social security, polypharmacy, acute or chronic diseases, dental and oral health problems, physiological changes with aging, inability to shop alone, inability to eat alone, change in the sense of taste and smell.

The MNA test consists of 18 questions consisting of 6 screening and 12 evaluation questions. 15 of these 18 questions are verbal inquiries and the other 3 are anthropometric measurements. All nutritional scoring is done out of 30 points, and the nutritional status of the person is considered normal when a score of 12 or more out of 14 is obtained in the pre-interrogation section consisting of six questions. In this section, if the patient gets 11 points or less, the remaining 12 questions of the test are continued. A total of 24-30 points is considered as a normal nutritional status, 17-23.5 is considered as at risk of malnutrition, and 17 and below is considered

malnutrition. The 15 verbal questions included in the MNA test are for the patient's general nutritional assessment and dietary habits. Anthropometric measurements made during MNA are as follows; BMI, upper arm circumference and calf circumference.[10-12] The Turkish validity and reliability study of the MNA test was conducted by Sarıkaya in 2013.[9]

At the first visit, the researchers in the research team informed the patient and/or caregiver about the study. At the first interview, the MNA test, which is routinely applied to all patients receiving home care service, whether they agreed to participate in the study or not, was filled in by obtaining information from the patient and/or caregiver. The test was implemented by using the face-to-face interview method. The upper arm circumference and calf circumference of the patient in the test were measured by the investigator with a tape measure. At this stage, procedures such as the prescribing formula for those who were found to have malnutrition or risk of malnutrition were performed.

At the second visit, which was made at least six months later, the patients who agreed to participate in the study were administered the MNA test, as well as a questionnaire created by the researchers regarding the sociodemographic data of the patient and the factors affecting nutrition.

Data were analyzed by IBM SPSS (Statistical Package for Social Sciences) ver. 22 package program. Continuous variables were represented as mean ± standard deviation, median (minimum and maximum values), and categorical variables were represented as numbers and percentages. The suitability of the data to the normal distribution was examined by the Kolmogorov-Smirnov test. Student's t-test was used to compare the mean MNA scores while examining the distribution of nutrition levels according to the MNA results of the first and second visits; and the Pearson Chi-square test was used to compare other changes between groups. In all analyses, $p<0.05$ was considered statistically significant.

Results

The ages of 320 patients included in the study ranged from 14 to 98 years, with a median age of 81.00 (IQR=13) years. Of the study population, 12.19% (n=39) were under 65 years of age, 32.81% (n=105) were between 65-79 years of age, and 55,00% (n=176) were aged 80 and over. While 84.06% (n=269) of the caregivers were first- and second-degree relatives such as spouses, children, siblings, grandchildren, and daughters-in-law, 15.94% (n=51) consisted of caregivers and other relatives who provide care in return for a salary. When the distribution of diseases that are the reason for receiving home care services is examined, the highest rate is 50.32% of neurological diseases (n=161). Some descriptive features of the patients included in the study are given in Table 1.

Table 1. Some Descriptive Features of the Patients Included in the Study

FEATURES		n	%
Gender	Male	106	33.13
	Female	214	66.87
Relationship degree of caregiver	Closely related	269	84.06
	Salaried employee	51	15.94
Primary diagnosis causing home dependency	Alzheimer-Parkinson-Dementia	82	25.63
	Cerebrovascular accident	79	24.69
	Orthopedic pathologies	44	13.75
	Cardiovascular pathologies	30	9.38
	Elderliness	38	11.88
	Endocrine and metabolic disorders	9	2.81
	Other diseases	38	11.88
The patient's method of nutrition	Normal oral feeding	238	74.38
	With formula	80	25.00
	Percutaneous Endoscopic Gastrostomy	2	0.63
Dependency level in the first interview	Totally confined to bed	99	30.94
	Mobile with wheelchair in the home	49	15.31
	Mobile with help at home	172	53.75

The mean total MNA score of the patients included in the study decreased statistically significantly between the two visits ($p<0.001$). Likewise, a statistically significant increase was determined in the number of patients evaluated as malnourished at the second visit compared to the other groups ($p<0.001$). The distribution of the nutritional level of patients according to first and second-visit MNA results is given in Table 2.

When examining the category of the patients in the classification made according to the descriptive characteristics asked in the study and the MNA values obtained at the first and second visits, a statistically significant difference was found in terms of deterioration of nutritional status in all characteristics, except for an endocrine and metabolic disorder ($p=0.165$) that caused the primary diagnosis to be home dependent ($p<0.001$ for all characteristics), nutritional status at first and second visits according to descriptive characteristics of patients receiving home health care are given in Table 3.

Table 2. Distribution of Nutritional Level of Patients According to First and Second Visit MNA Results

	First visit	Second visit	*p*
MNA score (mean±sd)	18.08±6.55	17.80±6.30	<0.001*
With malnutrition (%)	122 (38.13)	134 (41.88)	<0.001**
Under The Risk of Malnutrition (%)	121 (37.81)	113 (35.31)	
Normal (%)	77 (24.06)	73 (22.81)	

*Student's t-test **Pearson's Chi-square test

Table 3. Nutritional Status at First and Second Visits According to Descriptive Characteristics of Patients Receiving Home Health Care

		MNA first visit data						MNA second visit data						
		Normal		Under the Risk of Malnutrition		With malnutrition		Normal		Under the Risk of Malnutrition		With malnutrition		
FEATURES		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**P***
Gender	Male	22	20.75	38	35.85	46	43.40	23	21.70	36	33.96	47	44.34	<0.001
	Female	55	25.70	83	38.79	76	35.51	50	23.36	77	35.98	87	40.65	<0.001
Relationship degree of caregiver	Relative	63	23.42	103	38.29	103	38.29	63	23.42	97	36.06	109	40.52	<0.001
	Salaried	14	27.45	18	35.29	19	37.26	10	19.61	16	31.37	25	49.02	<0.001
Method of nutrition	Normal oral feeding	76	31.93	113	47.48	49	20.59	72	30.25	102	42.86	64	26.89	<0.001
	With formula	1	1.25	7	8.75	72	90.00	1	1.25	11	13.75	68	85.00	
	Percutaneous Endoscopic Gastrostomy	0	0.00	1	50.00	1	50.00	0	0.00	1	50.00	1	50.00	
Dependency level	Totally dependent	8	8.08	24	24.24	67	67.67	3	3.03	25	25.25	71	71.71	<0.001
	Mobile with wheelchair	8	16.33	23	46.94	18	36.73	11	22.45	22	44.90	16	32.65	<0.001
	Mobile with help	61	35.47	74	43.02	37	21.51	59	34.30	66	38.37	47	27.33	<0.001
Primary diagnosis causing home dependency	Alzheimer-Parkinson-Dementia	9	10.98	26	31.71	47	57.32	7	8.54	30	36.59	45	54.88	<0.001
	Cerebrovascular accident	20	25.32	36	45.57	23	29.11	16	20.25	34	43.04	29	36.71	<0.001
	Orthopedic pathologies	13	29.55	20	45.45	11	24.44	14	31.82	16	36.36	14	31.82	<0.001
	Cardiovascular pathologies	11	36.67	13	43.33	6	20.00	16	53.33	7	23.33	7	23.33	<0.001
	Elderliness	11	28.95	12	31.58	15	39.47	11	28.95	11	28.95	16	42.11	<0.001
	Endocrine and metabolic disorders	4	44.44	5	55.56	0	0.00	2	22.22	6	66.67	1	11.11	0.165
	Other diseases	9	23.68	9	23.68	20	52.63	7	18.42	9	23.68	22	57.90	0.001

*Pearson chi-square

When patients and caregivers were asked to rate the factors affecting the patient's nutrition between 1 and 5 according to their importance (1 = least important / 5 = most important), it was observed that the most important factor was the presence of existing disease with a score of 4.48± 0.71. Ranking of the importance given to the factors affecting nutrition by patients and caregivers and their scores are given in Table 4.

Table 4. Ranking of the Importance Given to the Factors Affecting the Nutrition by Patients and Caregivers and the Relationship of the Determined Factors with the Malnutrition Indicator Score

			Relationship of the Determined Factors with the Malnutrition Indicator Score			
	Given score		First examination		Second examination	
Factors Affecting Nutrition	**Mean±sd**	**Median**	**Coefficient***	***p***	**Coefficient***	***p***
Existence of patient	4.48 ± 0.71	5	-0.168	0.003	-0.117	0.036
Low functional status	4.14 ± 0.88	4	-0.134	0.017	-0.123	0.028
Effects of aging	3.71 ± 1.01	4	0.128	0.022	0.144	0.010
Inability to eat alone	2.86 ± 1.71	3	-0.594	<0.001	-0.543	<0.001
Inability to eat	2.70 ± 1.70	3	-0.648	<0.001	-0.665	<0.001
Polypharmacy	2.69 ± 1.57	3	0.248	<0.001	0.195	<0.001
Economic problems	2.58 ± 1.50	3	-0.070	0.214	-0.108	0.055
Low dietary intake	2.07 ± 1.55	1	-0.087	0.120	-0.088	0.115
Dental/oral health disorder	1.92 ± 1.40	1	0.153	0.006	0.130	0.020
Inability to cook	1.83 ± 1.29	1	-0.046	0.408	-0.072	0.197
Change in the sense of taste/smell	1.82 ± 1.26	1	0.052	0.358	0.026	0.640
Lack of support by the caregiver	1.64 ± 1.38	1	-0.117	0.036	-0.172	0.002
Inability to shop alone	1.54 ± 1.15	1	-0.040	0.480	-0.091	0.104
Not having social security	1.39 ± 1.12	1	-0.098	0.079	-0.158	0.005

*Pearson correlation Coefficient

Discussion

In this study, the nutritional status of individuals receiving health services at home was evaluated with the MNA test, and biopsychosocial factors affecting nutrition were dwelled on.

The mean MNA score of the individuals participating in the study was 18.08±6.55 on the first visit and 17.80±6.30 on the second visit. It was determined that the MNA total scores between visits decreased statistically to a significant extent. In a meta-analysis carried out by Pauly et al. in 2007, studies on nutritional status screening with MNA in nursing homes between 1999 and 2006 were reviewed. In 12 studies conducted

with MNA, malnutrition risk was found at rates ranging from 2% to 38%, and malnutrition risks at rates ranging from 37-62%. [13] In a newer cross-sectional study conducted in Turkey, the risk of malnutrition in the elderly individuals living in nursing homes evaluated with MNA, the malnutrition risk was reported as 37%.[14] In our study, 38.13% of the patients participating in the study were found to be malnourished, while the prevalence of malnutrition risk was found to be 37.81%. Although these results can be evaluated in accordance with the studies conducted in general, it was a remarkable finding that the rate of patients at risk of malnutrition was lower than in other studies, but the cases with malnutrition were compatible with high rates. We think that this finding may be due to the low socioeconomic level of our patients and their inability to access healthy food sources.

In a study by Ülger et al. in which the malnutrition status and related factors of 2327 patients aged 65 and over were evaluated, they identified five factors highly associated with malnutrition as female gender, depression, dementia, congestive heart failure, and decubitus ulcer presence.[14] In a systematic review study carried out by Tamura et al. in 2013. They examined the factors associated with weight loss, low BMI and malnutrition in the elderly staying in long-term care institutions. According to the results of the study, they found that depression, swallowing and chewing problems, poor oral intake, and dependence on nutrition were associated with weight loss.[15] According to the study by Bell et al. conducted on the patient staying in the nursing home, malnutrition, depression, cognitive disability, functional disability, and chewing difficulties were found to be related.[16]

In the study carried out by Johansson et al. with 579 home care patients, advanced age, low self-care, and the presence of depression were found to be three notable factors in the development of malnutrition.[17]

A recent review stated that older adult's dietary pattern is influenced by socioeconomic factors, price of food items, marital status, psychological factors, changes in sensory functioning, access to food commodities, nutrition knowledge and cooking skills, gastrointestinal problems, oral health and medication factors .[18]

In our study, the nutritional status of the participants was evaluated according to their gender, the closeness of the caregiver, level of dependence, and primary diagnosis of home dependency. Except for the endocrine and metabolic disorder as the primary diagnosis that caused him/her to be home dependent, all reasons were found to be important for the deterioration of his nutritional status. In the first meeting, the most important factors affecting nutrition by the patients and caregivers were stated as the presence of the disease, low functional status, the effects of aging, inability to eat alone, inability to eat, polypharmacy, dental/oral health disorder, and the caregiver's lack of support. Additionally, during the second meeting, merely the factor of the absence of social security was added to these factors. The results of our study suggested that psychosocial factors, as well as biological factors, are effective in the risk of malnutrition seen in patients receiving home care.

Conclusion

Patients in need of home health services are a group prone to malnutrition, especially when they are elderly or have chronic, mental, or physical diseases. The general health status, quality of life, and complications related to diseases will be positively affected by screening the patients with convenient scales, identifying those with malnutrition and those at risk of malnutrition with further examinations, and improving their nutritional status with appropriate interventions. In order to prevent the risk of malnutrition, we recommend the implementation of an adequate, balanced and healthy diet plan, regular monitoring of body weight and screening of nutritional status as frequently as possible with appropriate scales so that weight loss can be noticed promptly.

Ethical Considerations: This study was carried out after the approval of the Clinical Research Ethics Committee of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, dated 06.11.2017 and numbered 42/09.

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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ASSESSMENT OF SLEEP QUALITY AND ANXIETY LEVELS OF INDIVIDUALS WHO ARE IN HOME ISOLATION DUE TO THE COVID-19 PANDEMIC

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Abstract

Objectives: This study aimed to evaluate individuals' sleep quality and anxiety levels in home isolation during the coronavirus disease 2019 (COVID-19) pandemic.

Materials and Methods: The study was planned in a descriptive cross-sectional design and was conducted between 01.07.2020–31.07.2020 with 186 individuals who were isolated at home due to contact with infected people and due to being infected with COVID-19. The subjects were asked to complete a sociodemographic data form, the Beck Anxiety Inventory and the Pittsburgh Sleep Quality Index.

Results: The mean Pittsburg Sleep Quality Index was 5.33, and the number of participants with poor sleep quality was found to be 92 (49.46%). A significant correlation was found between sleep quality and anxiety scores ($r=0.705$; $p<0.001$). Female participants who were infected with COVID-19 had higher anxiety scores (mean Beck Anxiety Inventory score: 8.93) and worse sleep quality (mean Pittsburg Sleep Quality Index score: 6.11, $p = 0.002$).

Conclusion: The COVID-19 Pandemic affected anxiety and sleep quality in those isolated at home. This situation is more common among female participants and those confirmed as COVID-19 positive via RT-PCR (Reverse Transcription Polymerase Chain Reaction).

Keywords: Anxiety, COVID-19, sleep quality.

Introduction

The World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020.[1] To combat the pandemic, restrictions were imposed worldwide, and measures were taken to minimize contact with infected individuals.[2] One of these measures in Turkey is home isolation. Isolation is the segregation of patients with infectious diseases to protect uninfected persons. Depending on the patient's diagnosis and symptoms, it can be done in the hospital or at home. Home isolation is appropriate for patients with adequate facilities to be adequately cared for at home and who can recover without sharing an area close to uninfected persons.[3,4]

The pandemic period and associated restrictions, such as isolation, have undoubtedly affected people both financially and morally. Most "individuals isolated at home due to treatment " (IIDT) or "individuals isolated at home due to contact " (IIDC) suffer from anxiety and worry because there is no specific treatment for the disease.[5] In addition to these worries, the absence of loved ones and lack of social contact due to the restrictions can cause symptoms such as loneliness, hopelessness, stress, and anxiety. COVID-19-related mental health problems also affect sleep.[6]

Sleep is essential to our mental and physical health.[7] Sleep quality is an important indicator that affects a person's cognitive and physical abilities, as well as his/her social life. There are many factors that affect sleep quality; the most common are smoking, afternoon coffee consumption, alcohol consumption, sleep hygiene disorders, stress and anxiety, and additional illnesses.[8]

Because so many factors affect sleep quality, it is becoming increasingly important to study sleep quality and know the factors that affect it during the pandemic.

This study aimed to examine sleep quality and anxiety levels, as well as some influencing factors, in individuals isolated at home due to treatment (IIDT) or individuals isolated at home due to contact (IIDC) during the COVID-19 pandemic.

Materials and Methods

Study population and sample

Our study was planned as a descriptive cross-sectional study and was conducted between 01/07/2020 and 31/07/2020 in Istanbul Esenyurt Central Family Health Center and Sultangazi Family Health Training Center No. 1 and No. 2. Since the mean number of individuals isolated at home due to treatment (IIDT) and contact

(IIDC) between May and June was 298, the sample size was calculated to be 169 with a confidence interval of 95%.

Patients who were isolated at home between May and June were contacted by telephone and informed about the study. The survey included 186 individuals who agreed to participate in the study and completed the questions in full. Individuals with a known psychiatric disease prior to the pandemic and individuals being treated for sleep disorders were not included in the study.

Data collection tools

The questionnaire used in the study was designed by the researchers based on recent articles. In addition to questions on sociodemographic and background data and information on home isolation, the Pittsburg Sleep Quality Index (PSQI) was used to measure sleep quality, and the Beck Anxiety Inventory (BAI) was used to measure participants' anxiety levels.

PSQI

The PSQI questionnaire consists of 19 items with seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. It is used to assess sleep over a 1-month interval. Each component is weighted equally on a scale of 0 to 3. All components are summed to give a total score between 0 and 21. Higher scores indicate poorer sleep quality. A total score ≥5 indicates poor sleep quality. Agargun et al. have shown that the PSQI is valid in Turkish population samples.[9]

BAI

The BAI is used to assess the frequency of anxiety symptoms in individuals. It is a Likert (sum of degrees) measure. There are four options for each of the 21 symptom categories. Each item is given a score between 0 and 3. High scores on the scale indicate the severity of anxiety experienced by the person. The patient is asked to rate his/her symptoms in the "last week, including the same day." The total score ranges from 0 to 63. The suggested values are as follows: 0-7 represents minimal anxiety, 8-15 represents mild anxiety, 16-25 represents moderate anxiety, and 26-63 represents severe anxiety. Studies have shown that BAI is reliable and valid for Turkish population samples.[10]

Statistical analysis

The SPSS program was used for statistical analysis. For descriptive data analysis, number and percentage (n, %) were presented for categorical variables, while mean, standard deviation and minimum and maximum values were presented for numerical variables. The chi-square test was performed to compare categorical data in independent groups, and Student's T-test was performed to compare numerical data in independent groups. Correlation values were determined using the Pearson correlation coefficient test. The statistical significance level of alpha was accepted as $p < 0.05$.

Results

The study was conducted with 186 participants who were isolated at home due to treatment (n=96) or preventing contact (n=90). Analysis of sociodemographic and background data is shown in Table 1.

Sleep quality data

The mean PSQI score of participants in this study was 5.33. In our study, we found that 94 (50.54%) individuals had good sleep quality (PSQI scores of 0-4), whereas 92 (49.46%) participants with PSQI scores more than 5 had poor sleep quality. PSQI subgroup scores are given in Table 2.

We investigated the effects of sociodemographic factors on sleep quality. There was a significant association between age and PSQI scores, and we observed an increase in PSQI scores with increasing age ($r=0.17$, $p=0.02$). While the mean PSQI score of single participants was 3.65, it was 5.92 for married participants. The sleep quality of single participants was better, and the difference was statistically significant ($p<0.01$). The mean PSQI score in females and males was 6.11 and 4.45, respectively, and the difference was statistically significant ($t=3.080$ $p=0.002$). It was also found that PSQI score did not differ by chronic diseases ($t=0.16$ $p=0.98$), alcohol consumption ($t=-1.490$ $p=0.13$), living alone at home ($t=-0.546$ $p=0.4$), and whether participants had an active working life or not ($t=-1.675$ $p=0.095$). Analysis of PSQI scores by reasons for isolation at home is presented in Table 3.

Table 1. The evaluation of the sociodemographic and background data (n=186)

Variables	Categories	% (n)
Age	18-64	95.16 (177)
	65 +	4.84 (9)
Gender	Female	53.23 (99)
	Male	46.77 (87)
Marital status	Not Married	25.81 (48)
	Married	74.19 (138)
Employment status	Working	47.85 (89)
	Not Working	52.15 (97)
Alcohol consumption	Yes	8.61 (16)
	No	91.39 (170)
Smoker	Yes	25.81 (48)
	No	74.19 (138)
Diagnosed with a chronic disease	Yes	22.04 (41)
	No	77.96(145)
Living alone	Yes	3.76 (7)
	No	96.24 (179)

Table 2. PSQI subgroup scores

PSQI subgroups	0 n (%)	1 n (%)	2 n (%)	3 n (%)	Mean Score
Subjective Sleep Quality	40 (21.51)	85 (45.69)	48 (25.81)	13 (6.99)	1.18
Sleep Latency	46 (24.73)	57 (30.64)	47 (25.27)	36 (19.36)	1.4
Sleep Duration	109(58.60)	52 (27.96)	18 (9.68)	7 (3.76)	0.59
Habitual Sleep Efficiency.	153(82.26)	26 (13.98)	7 (3.76)	0	0.22
Sleep Disturbances	33 (17.74)	119(63.98)	31 (16.67)	3 (1.61)	1.02
Use of Sleeping Medication	163(87.63)	9 (4.84)	9 (4.84)	5 (2.69)	0.23
Daytime Dysfunction	108(58.07)	34 (18.28)	33 (17.74)	11 (5.91)	0.72

Table 3. The evaluation of sleep quality according to the reasons for isolation at home

	Individuals who are confined to isolation at home due to treatment (ICIDT) n=96 Mean Score	Individuals who are confined to isolation at home due to contact with infected people (ICIDC) n=90 Mean Score	t	p
Subjective Sleep Quality	1.47	0.88	**5.039**	**<0.001***
Sleep Latency	1.71	1.07	**4.265**	**<0.001***
Sleep Duration	0.67	0.50	1.396	0.16
Habitual Sleep Efficiency	0.28	0.14	1.895	0.06
Sleep Disturbances	1.22	0.81	**4.595**	**<0.001***
Use of Sleeping Medication	0.28	0.17	1.185	0.23
Daytime Dysfunction	1.00	0.41	**4.390**	**<0.001***
PSQI total score	6.61	3.97	**5.120**	**<0.001***

* Independent Samples T Test

Anxiety scale data

The proposed rating scores for the Beck Anxiety Scale are as follows: 0-7 represents minimal anxiety, 8-15 represents mild anxiety, 16-25 represents moderate anxiety, and 26-63 represents severe anxiety. The mean BAI score of participants was 7.56 ± 6.98 (minimum: 0, maximum: 38), which corresponds to minimal anxiety. Of the participants, 59.68% (n=111) had minimal anxiety, 23.66% (n=44) had mild anxiety, and 16.67% (n=31) had moderate and severe anxiety. When examining the association between anxiety level and sociodemographic data, no significant correlation was found between age and anxiety level (r=0.11, p= 0.13). However, female participants were found to have higher anxiety levels than males, with anxiety scores of 8.93 and 6.01, respectively, and the difference was statistically significant (t=2.901 p=0.004).

The mean score of BAI was 8.19 for married and 5.77 for single; the difference was statistically significant (t=2.085 p=0.02). The mean anxiety level of IIDT was 10.49 ± 7.23 (minimum: 0, maximum: 38), and that of IIDC was 3.85 ± 4.41 (minimum: 0, maximum: 21). The difference was statistically significant (t=-7.288 p<0.001). The assessment of anxiety levels according to the reasons for isolation at home is shown in Figure 1. A significant correlation was found between sleep quality and anxiety scale (r=0.705; p< 0.001). In addition, participants were divided into two groups according to their sleep quality. A PSQI score of more than 5 represents poor sleep quality, and a score of 0-4 represents good sleep quality. Anxiety levels were compared between the two groups (Figure 2). It was found that individuals with poor sleep quality had more moderate and severe anxiety symptoms (p<0.001).

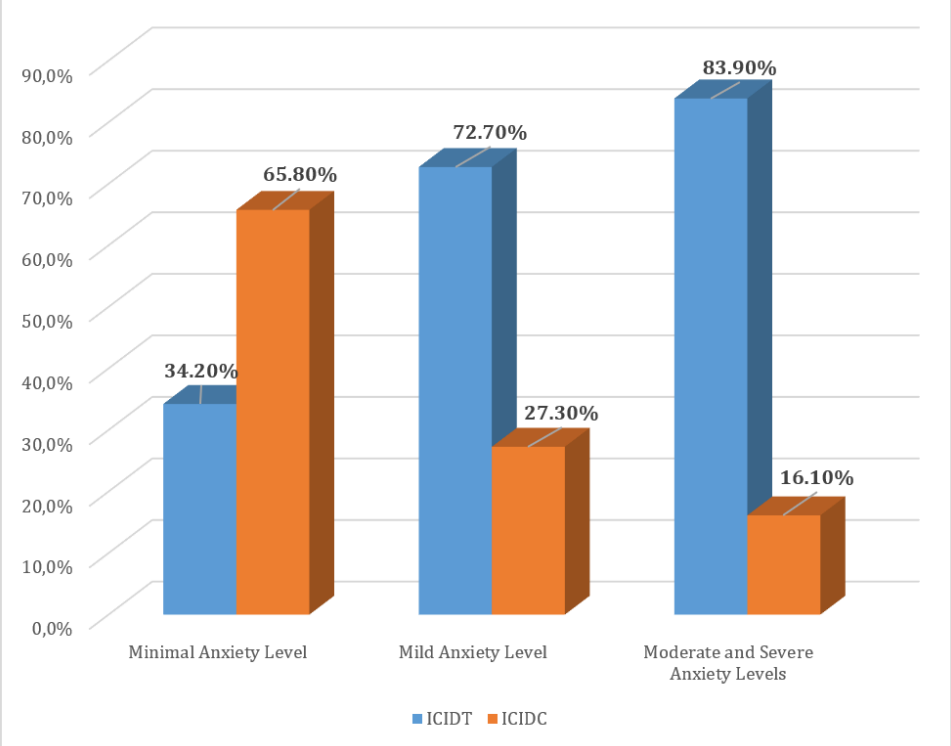

Figure 1. The evaluation of anxiety level according to the reasons for isolation at home

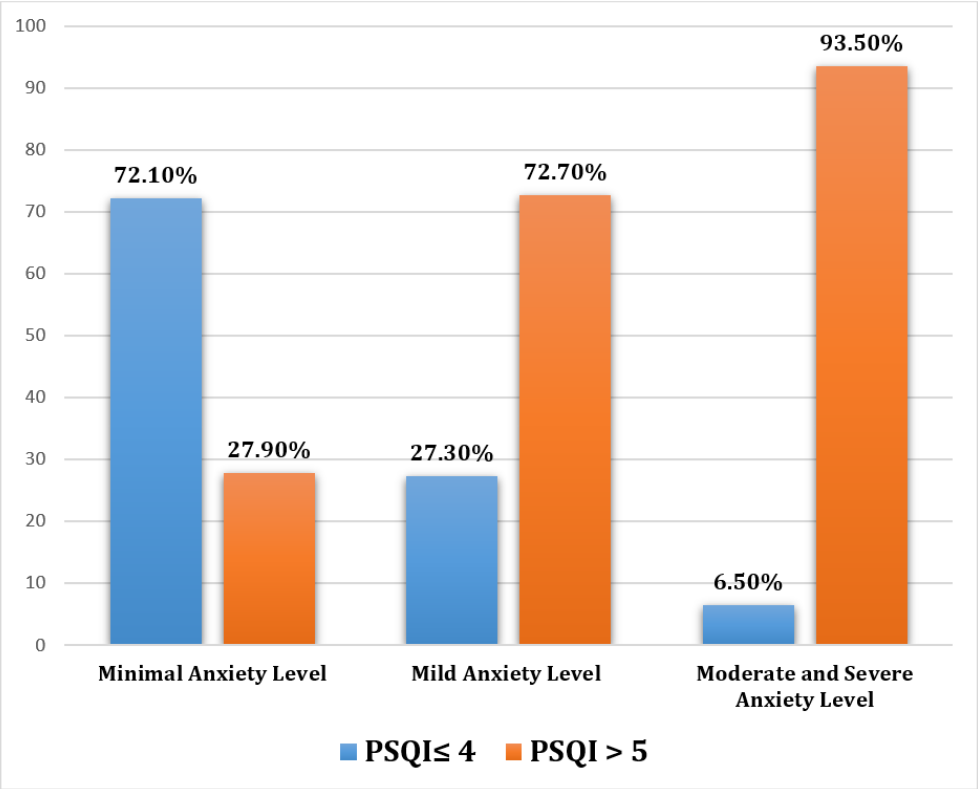

Figure 2. Correlation between sleep quality and anxiety scale

Discussion

Measures such as social distancing, travel restrictions, curfews, and home isolation were taken to control the COVID-19 pandemic.[11,12] Home isolation and quarantine due to COVID-19 may have different effects on sleep, which plays an important role in psychiatric disorders.[13] Patients with sleep disturbances are likely to have more symptoms during home isolation.[14] In a study examining the prevalence of mental health symptoms and related factors during the COVID-19 Pandemic in China, it was determined that nearly one-third of respondents suffered from anxiety and insomnia symptoms.[15] In another study, it was observed that exposure to uncontrollable or unpredictable stressors such as hurricanes, earthquakes, and tsunamis resulted in poorer sleep quality.[16] In our study, nearly half of the participants had sleep disorders, and their anxiety levels were mostly minimal.

There are studies showing that females are more likely to suffer from insomnia during the pandemic.[17] The sleep quality of the female participants in our study was also poor. This could be due to the fact that female participants in our study were more likely to suffer from anxiety, which is thought to affect sleep quality. There are studies reporting that symptoms related to anxiety, depression, and panic disorders resulting from social

isolation and long-term quarantine, which are part of pandemic measures, are more common in females.[11,18,19] Female reproductive hormones and associated cycles have been shown to play an important role in gender differences.[20] Living alone or being alone might negatively affect sleep quality; however, this association is often linked to depression and stress from loneliness.[21] Therefore, sleep quality might not be affected in people who live alone but do not feel lonely, causing less stressful changes in isolation and daily routines compared with people who live with a family or partner. In our study, this could explain the fact that people living alone have less anxiety and better sleep quality. In this study, married participants also had more anxiety and poorer sleep quality than single participants.

Sleep disturbances are common in patients with cancer and chronic medical conditions.[22] However, in our study, there was no difference in anxiety and sleep disturbances between people with chronic diseases and those without chronic diseases, which may reflect the intensity of uncertainty and problems caused by the pandemic. A study conducted in Canada suggested that demographic factors such as marital status, age, education, living with other adults, and having children are not associated with the psychological consequences of those quarantined due to the severe acute respiratory syndrome (SARS) epidemic; these findings support our study.[23]

There are also studies suggesting that home isolation reduces levels of physical activity and exposure to daylight and that social isolation increases stress levels, such as due to lack of social contact with family and friends, and disrupts nighttime sleep.[18] A study conducted in China found a significant difference in anxiety levels between those who were quarantined for COVID-19 and those who were not.[24] Another study conducted in China found that isolated individuals had high levels of anxiety and stress, and their sleep quality was low.[5] A study conducted in Italy reported that the deterioration in sleep quality was more pronounced in individuals with depression, anxiety, and stress symptoms.[25] Similarly, a study conducted in central China with people who were isolated at home for 14 days showed that worsening sleep quality was associated with an increase in anxiety and stress.[5] Similarly, in our study, we found that isolated people suffered from anxiety and sleep problems; however, the type of isolation is important in this regard. We concluded that IIDT had significantly more moderate and severe anxiety symptoms and poorer sleep quality. A previous study had shown that an early COVID-19 test is a risk factor for depression.[26]

The problems faced by isolated individuals, especially IIDT, are more frequent and may cause them to delay treatment, which can jeopardize both individual and societal health.

To prevent this situation, IIDC should be advised to continue their daily lives as much as possible and engage in enjoyable and relaxing activities and exercises that they can do at home.

The study has some limitations. Because the analyses were not conducted over a long period of time, it was not possible to determine the evolution of anxiety and insomnia during the different phases of the pandemic, which depended in part on which variables were affected. Because the pre-pandemic situation of the participants in terms of anxiety and sleep quality was not known, no comparison could be made.

The COVID-19 pandemic affected anxiety and sleep quality in those isolated at home. This situation is more common among female participants and those confirmed as COVID-19 positive via RT-PCR.

Ethical considerations: The local clinical research ethics committee approved the study (Approval No. 2865, dated 30/06/2020).

Conflict of Interest: The authors declare that there are no potential conflicts of interest related to the research, authorship, and/or publication of this article.

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Research Article

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ASSOCIATION OF REACTIVE HYPOGLYCEMIA WITH BODY MASS INDEX, HOMEOSTATIC MODEL ASSESSMENT OF INSULIN RESISTANCE AND COMORBIDITY

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Abstract

Objectives: Untreated hypoglycemia at profoundly low levels restrains the delivery of energy to vital organs and causes a series of extreme adverse events, ultimately resulting in coma and death. The purpose of the study was to determine the relationship between body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR), and co-morbidities in patients experiencing hypoglycemia during an oral glucose tolerance test (OGTT).

Materials and Methods: We retrospectively analyzed the medical records of all patients presented to the diet outpatient clinic between 2015 and 2020 for OGTT. After an overnight fast of 10-12 hours, the patient's fasting insulin (HOMA-IR) and fasting glucose were recorded. A 330cc solution of glucose (containing 75 grams of dextrose anhydride) drink was used for the OGTT. Following this, blood glucose was measured at 30, 60, 120, 180, and 240 minutes. The obtained data were analyzed using descriptive and inferential statistics.

Results: A total of 614 patients were analyzed. A positive correlation was found between BMI and HOMA-IR ($p \leq 0.001$), BMI and blood glucose ($p \leq 0.001$). Although hypoglycemia rates were higher in overweight and obese patients, the difference was not significant ($p = 0.316$). The presence of co-morbidity did not affect the incidence of hypoglycemia ($p = 0.413$).

Conclusion: We observed that increased BMI was associated with having HOMA-IR and high glucose levels at 0-30-60-120 minutes in OGTT. Although hypoglycemia during the OGTT was not associated with BMI in this study, large-scale studies are needed to reveal this relationship.

Keywords: Glucose tolerance test, reactive hypoglycemia, insulin resistance.

Introduction

Glucose, the main source of energy for the body, plays an integral role in maintaining the dynamic balance of the body. According to the American Diabetes Association, a fasting plasma glucose value between 70 to 99 mg/dL (3.9 mmol/L-5.5 mmol/L) is considered normal.[1] Any variation in these values results in either hypoglycemia or hyperglycemia, each with its own significant consequences. During the initial phases of hypoglycemia (<70-54 mg/dL), a series of autonomic nervous symptoms are observed, including tachycardia, tremor, sweating, nausea, and hunger. With the further reduction of blood glucose (<54 mg/dL), there is a loss of energy supply to vital organs resulting in confusion, dizziness, lethargy, seizures, coma, and sudden death.[1-3] Reactive or biochemical hypoglycemia is a postprandial hypoglycemic state that mostly occurs after 2-5 hours of food intake.[4,5] Possible mechanisms include insulin resistance in combination with inappropriately high insulin levels, impaired insulin clearance, and insulin hypersensitivity.[6,7]

Although reactive hypoglycemia does not attract attention, if left untreated, it may result in emotional disturbances, irritability, risk of trauma due to falls or road traffic accidents, and sudden death.[2,8] Despite the increased prevalence of reactive hypoglycemia during oral glucose tolerance test (OGTT) among the general population (0.53-50%), there are limited studies available that focus on the factors associated with these hypoglycemic episodes.[4,9-11] Hence, the present study was carried out to determine the association between body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR) and the presence of co-morbidity in people with hypoglycemic episodes during OGTT.

Materials and Methods

A retrospective study was carried out to analyze the medical records of patients who visited the Diet outpatient clinic for OGTT between 2015 and 2020. The study was approved by the institutional ethical committee. All patients with symptoms of hypoglycemia regardless of weight, patients who experienced rapid weight gain (at least 1.50 kg per month for three months within the past year) with mild or no symptoms of hypoglycemia and those patients with a pre-diagnosis of hypoglycemia were included in the study. Children ≤14 years of age, pregnant women, patients with gradual weight gain (in more than a year), patients with diabetes, those using an antidiabetic medication, or patients unable to continue the test due to their hypoglycemic symptoms such as nausea, vomiting, and low blood pressure within the first hour of OGTT were excluded from the study. Informed consent was obtained prior to the test. The patient's age, sex, height, and weight were recorded before the test. Height and weight for BMI were measured using a stadiometer (model 240, Seca, Germany) and a digital scale (WB-300 Plus, Tanita, Japan).

Patients were instructed not to consume food after 22.00 hours on the previous night and fast for at least 10 hours prior to the test. Water intake of only one glass was permitted, if necessary. A single antecubital intravenous catheter was inserted for blood sampling. At the 0th minute, blood was drawn to check fasting glucose and insulin. An apple-flavored glucose drink (Glucosol)® containing 91 kcal in 100 cc solution was used for the OGTT. The patients were asked to drink measuring 330 ccs containing 82.50 grams of dextrose monohydrate, equivalent to a total of 75 grams of dextrose anhydride. Following this, blood samples were drawn at 30 min, 60 min, 120 min, 180 min, and 240 min to check blood glucose levels. Glucose was measured by the hexokinase enzymatic method using a gel tube with the Beckmann Coulter AU480 instrument. Insulin was measured with the Chemiluminescence method with the Beckmann Coulter Access2 instrument using a gel tube.

Definition of variables

The blood glucose level of < 70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L) was considered as the cut-off value for hypoglycemia.[1] BMI was calculated as weight divided by height squared (kg/m^2), and patients were categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).[12] HOMA-IR was calculated by multiplying fasting glucose with fasting insülin divided by 405. Regardless of gender, a value ≥ 2.5 was considered significant, suggesting insulin resistance.[13] The association of the following co-morbidities with hypoglycemia was studied: hypothyroidism, unspecified (E03.9), anxiety disorder, unspecified (F41.9), headache (R51), essential (primary) hypertension (I10), asthma (J45), excessive, frequent and irregular menstruation (N92), dizziness and giddiness (R42) (based on the ICD-10 Version-2019).[14]

Statistical analysis

The obtained data were entered in Microsoft Excel and analyzed using SPSS version 23. The descriptive statistics were expressed in terms of number and percentage. The continuous variables were compared using a one-way analysis of variance (ANOVA) test followed by Tukey's Post Hoc Analysis, while the frequency of dichotomous variables was performed by Chi-Square analysis or Fischer Exact Test (as appropriate). Pearson's correlation coefficient was used to analyze the relation between two continuous variables. A two-sided $p \leq 0.05$ was considered significant.

Results

The present study analyzed 614 patients, 545 (88.76%) females and 69 (11.24%) males. The mean age of patients was 37.90 ± 10.83 years, and the mean BMI was 29.30 ± 5.40 kg/m^2. Among the 614 patients, 125

(20.36%) had normal BMI, 249 (40.55%) were overweight, and 240 (39.09%) were obese. The average fasting glucose was 93.40± 9.90 mg/dL. Fasting insulin was measured only in 365 patients; the mean fasting insulin was 9.70 ± 5.70 µIU /mL. Similarly, the average score of HOMA-IR among 365 patients was 2.3 ± 1.5. HOMA-IR of ≥ 2.5 was observed in 134 (36.71%) patients.

A positive correlation was found between BMI and HOMA-IR (p≤0.001) (Table 1). Additionally, the HOMA-IR in the normal weight and overweight patients was significantly different from the obese patients (Table 2). Similarly, a positive correlation was found between the BMI and glucose levels of patients. The higher the blood glucose, the BMI was found to be significantly higher (p≤0.001). Table 3 shows the difference in the BMI levels of patients at each blood sugar estimation phase. It was found that the blood glucose was significantly higher among obese patients at fasting (p=0.002), 30 minutes (p≤0.001), 60 minutes (p≤0.001), and 120 minutes (p≤0.001) as compared to other groups. However, at 180 minutes (p=0.181) and at 240 minutes (p=0.448), there was a decrease in blood glucose levels among obese patients.

During OGTT, blood glucose was examined a total of 3684 times, that is six times in 614 patients each. Among these patients, hypoglycemia was detected in 344 patients (56.02%) 421 times (11.42%). A higher incidence of hypoglycemia (90.94%) was observed between 180 and 240 minutes during OGTT. Of these, 78.82% of hypoglycemia occurred in patients with a BMI of ≥25. Blood glucose levels between 54 and 70 mg/dL, suggesting 1st-degree hypoglycemia, were observed in 294 (85.43%) patients at 371 (88.11%) times. 2nd-degree hypoglycemia was characterized by a blood glucose value of <54 mg/dL observed in 50 (14.64%) patients at 50 (11.91%) times. Hyperglycemia (≥200 mg/dL) and hypoglycemia (<70 mg/dL) occurred in the same case in 33 (5.37%) patients. Most of the patients (270, 44.0%) had a single episode of hypoglycemia, followed by two episodes in 71 (11.58%) patients, and three episodes were observed in 3 (0.49%) patients (Fig. 1). Multiple episodes were common in patients in the overweight and obese category as compared to normal weight; however, the difference was not statistically significant (p= 0.316). We observed a significant difference in the mean BMI levels regarding different recurrence rates of hypoglycemia (p=0.011) (Table 4).

In our study, a total of 181 (29.47%) patients had associated co-morbidities. Among them, hypoglycemia was observed in 106 (58.56%) patients (Fig. 2). The most common co-morbidity in patients with hypoglycemia was hypothyroidism (25.62%), followed by irregular menstruation (24.45%), anxiety disorder (18.46%), hypertension (12.77%), headache (10.93%), dizziness (3.93%), and asthma (3.86%). Among 270 patients with no hypoglycemia, co-morbidity was present in 76 (28.15%) patients. Irregular menstruation (27.34%) was the most common finding, followed by hypothyroidism (20.95%), anxiety disorder (19.13%), hypertension (15.21%), headache (9.86%), dizziness (5.02%) and asthma (3.16%). Co-morbidity was slightly higher in patients with hypoglycemia than in patients without hypoglycemia (30.84% versus 28.11%). We did not observe a significant association between the presence of co-morbidity with hypoglycemia (p=0.413) and also

with the frequency of hypoglycemic episodes (p= 0.568). Table 5 summarizes the presence or absence of hypoglycemia with the presence of co-morbidity and its association with BMI levels. Higher BMI was found in individuals who exhibited both hypoglycemia and co-morbidity; however, this difference was not statistically significant (p= 0.188).

Table 1. Association of BMI and HOMA- IR.

Group	n	Mean HOMA-IR	Std. Deviation	F	p
Normal Weight	50	1.79	0.90	13.434	≤0.001*
Overweight	159	2.03	1.19		
Obese	156	2.74	1.77		

(BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance)
*ANOVA test, the p-value is significant at <0.05

Table 2. Tukey's Post Hoc Analysis for checking the association of BMI and HOMA- IR.

(I) BMI	(J) BMI	Mean Difference (I-J)	Std. Error	p
Normal Weight	Overweight	-0.24	0.23	0.561
	Obese	-0.95*	0.23	≤0.001*
Overweight	Normal Weight	0.24	0.23	0.561
	Obese	-0.72*	0.16	≤0.001*
Obese	Normal Weight	0.95*	0.23	≤0.001*
	Overweight	0.72*	0.16	≤0.001*

(BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance)
*Tukey's Post Hoc Analysis. The mean difference is significant at the 0.05 level.

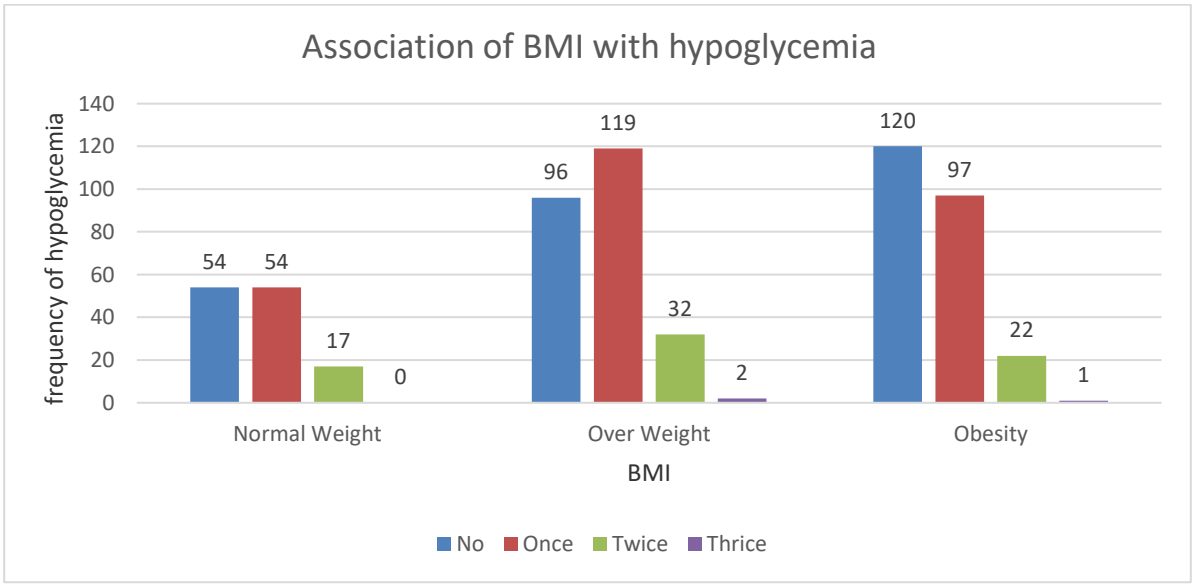

Figure 1. Bar diagram showing the frequency of hypoglycemic episodes with different grades of Body Mass Index (BMI).

Table 3. Association between BMI and Blood glucose levels at different intervals.

BMI *Blood glucose		n	Mean- Blood glucose	Std. Deviation	F	p
0 Minutes					6.238	0.002*
	Normal Weight	125	91.50	8.94		
	Overweight	249	92.76	9.54		
	Obese	240	95.05	10.60		
30 Minutes					14.872	≤0.001*
	Normal Weight	125	138.70	27.18		
	Overweight	249	146.35	28.49		
	Obese	240	154.96	27.54		
60 Minutes					24.404	≤0.001*
	Normal Weight	125	124.94	36.80		
	Overweight	249	136.29	38.98		
	Obese	240	153.43	40.46		
120 Minutes					15.780	≤0.001*
	Normal Weight	125	100.86	24.34		
	Overweight	249	108.18	29.00		
	Obese	240	118.06	31.34		
180 Minutes					1.716	0.181
	Normal Weight	125	77.34	21.07		
	Overweight	249	76.43	20.64		
	Obese	240	79.66	17.70		
240 Minutes					0.805	0.448
	Normal Weight	125	75.72	11.24		
	Overweight	249	75.95	9.98		
	Obese	240	76.96	10.53		

(BMI: Body Mass Index)
*ANOVA test, the p-value is significant at <0.05

Table 4. Correlation of Mean BMI with the frequency of hypoglycemia.

Hypoglycaemia	**n**	**Mean**	**Std. Deviation**	**F**	**p**
No	270	30.12	5.77	3.771	0.011*
Once	270	28.82	5.38		
Twice	71	28.19	4.30		
Thrice	3	28.47	1.75		

(BMI: Body Mass Index)
*ANOVA test, the p-value is significant at <0.05

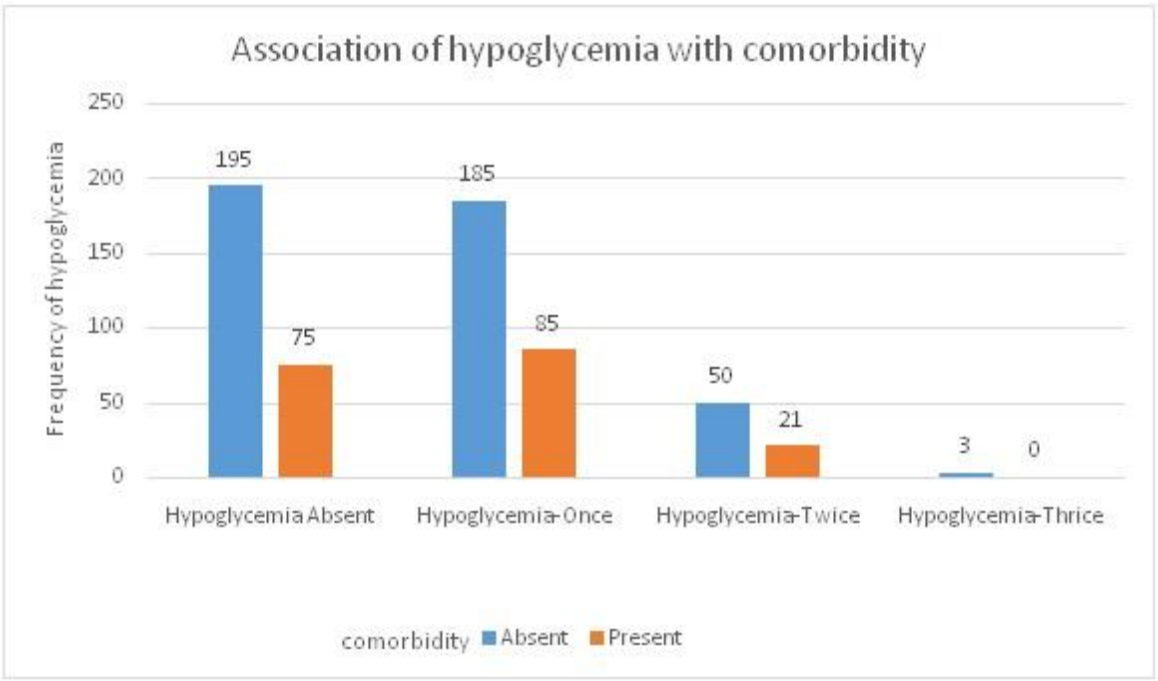

Figure 2. Bar diagram showing the frequency of hypoglycemic episodes in patients with co-morbidities.

Discussion

A drop in blood glucose levels below the normal limits after a few hours of food intake is known as reactive or biochemical hypoglycemia. Based on varying causes, it can either be idiopathic, alimentary, or diabetic. Regular insulin secretion with increased insulin sensitivity and the decreased response of glucagon are characteristics of reactive hypoglycemia.[4] Also, the presence of insulin resistance leads to basal-fasting hyperinsulinemia with subsequent insensitivity of beta-cell secretion. The resultant decrease or failure of first-phase insulin response results in exaggerated compensatory second-phase insulin secretion with resultant delayed hypoglycemia.[9] Although hypoglycemia is relatively rare finding as compared to hyperglycemia during OGTTs, it must not be ignored. Untreated hypoglycemia, especially the 2nd degree, characterized by profoundly low levels of blood glucose, is associated with increased morbidity and mortality.[8] In view of this, the present study was carried out to evaluate the association of hypoglycemia during OGTT with BMI, HOMA-IR, and the presence of co-morbidity.

The presence of clinical symptoms and low blood glucose during laboratory investigation and the reversal of symptoms with glucose ingestion confirms the diagnosis of hypoglycemia. However, the symptoms of hypoglycemia are unspecific, and there is a lack of a standardized questionnaire.[15,16] With a blood glucose cut-

off value of <70 mg/dL, the incidence of hypoglycemia in our study was 56.02%. Among these, 85.43% had 1st-degree hypoglycemia (between 54-70 mg/dL), and 14.64% had 2nd-degree hypoglycemia (<54 mg/dL). Incidence was much higher as compared to the previous studies in which the rates were between 0.53% and 5,0% at <54 mg/dL, between 12.3% and 46.6% at 70 mg/dL.[4,5,8,10,17] The difference in the incidence could be because of the variable cut-off values used in the definition of hypoglycemia. However, the incidence of hypoglycemia was higher in our study compared to the studies using <70 mg/dL as the cut-off value as well. This could be because our study cohort consisted of patients with a pre-diagnosis of hypoglycemia who either described symptoms of hypoglycemia themselves or OGTT was requested by the clinician with the pre-diagnosis of hypoglycemia because they gained weight in a short time.

In our study, increased BMI (>25 kg/m^2) was observed in 79.64% of patients. The mean age of the patients with hypoglycemia in our study was less (37.9 ± 10.8 years) as compared to the age reported by Cai et al. (42.5 ± 13.1 years), while the mean BMI was much higher (29.3±5, 42 vs. 2.8 ± 3.2 kg/m^2).[9] Previous studies have suggested that in Type 2 Diabetes Mellitus with an increased BMI, the severity of hypoglycemia decreases.[18] Elliott et al. and Alghamdi et al. suggested that low body weight is a strong predictor of hypoglycemia. It is believed that a lower BMI may partially reflect a state of malnutrition, which invariably increases the risk of hypoglycemia.[17-19] On the contrary, Lv et al. suggested a positive correlation between BMI and hypoglycemia.[2] In our study, the incidence of hypoglycemia was higher with increased BMI; however, the difference was statistically insignificant. Also, the frequency of hypoglycemic episodes was independent of BMI. Despite higher secretion of insulin, there was a gradual reduction in blood glucose in obese patients suggesting insulin resistance resulting in secondary hyperinsulinemia and lower blood glucose levels.[2]

According to Altuntas et al., hypoglycemia due to alimentary causes has an early onset (<120 minutes), while idiopathic hypoglycemia and diabetic hypoglycemia have late onset, commonly observed at 180th minutes and 240th-300th minutes, respectively.[4] We observed a higher incidence of hypoglycemia (90.94%) between the 180th and 240th minutes during OGTT. A positive correlation between BMI and blood glucose was observed in our study. Although higher blood glucose was observed in obese patients during the initial phases of OGTT, there was a decrease in blood glucose at 240th minutes. Our results are in accordance with Lv et al., who reported no significant difference in the fasting glucose levels between different BMI groups; however, they observed a sharp decline of glucose levels in the obesity group as compared to the normal and overweight groups.[2]

Basal hepatic glucose production reflecting hepatic insulin sensitivity is closely related to fasting blood glucose. Fasting glucose levels were higher in polycystic ovary syndrome cases with increased BMI, which explains the higher blood glucose observed in our study group. The decrease in insulin sensitivity in the form of late hypoglycemia occurring at 4 hours postprandial explains the hypoglycemia observed at 240th minutes.[4]

Insulin resistance, a risk factor for hypoglycemia and subsequent diabetes, affects 25% of the general population. Previous case reports have suggested that reactive hypoglycemia associated with insulin resistance and impaired glucose tolerance subsequently normalized after appropriate treatment.[20,21] This suggests that reactive hypoglycemia might be an indicator of early beta-cell dysfunction. Hyperinsulinemic-euglycemic clamp (HEC) is the gold standard for measuring insulin resistance; however, it is neither feasible nor cost-effective.[22] HOMA-IR used in our study is easy to calculate and effectively reflects insulin resistance. Higher levels of HOMA-IR were observed in patients with hypoglycemia, suggesting higher insulin resistance.[9] We observed insulin resistance in 36.7% of patients.

Similar to the findings by Awede et al. and Lv et al., a direct correlation between BMI and HOMA-IR was observed in our study.[2,23] To maintain blood glucose homeostasis, insulin secretion is higher in patients with a higher degree of insulin resistance, suggesting a direct correlation between insulin demand and weight gain. Moreover, these patients have decreased insulin sensitivity, which delays the secretion of insulin. A combination of increased insulin resistance and decreased insulin sensitivity results in delayed hypoglycemia.[24,25] On the contrary, Parekh et al. have suggested a mechanism of increased insulin sensitivity rather than insulin resistance resulting in hypoglycemia during 2-hour OGTT suggesting a lower diabetic risk; however, further studies were warranted in this regard.[10]

Excess fat mass and visceral adiposity are potential risk factors for diabetes and cardiovascular diseases, amongst others.[13] Previous studies have suggested an association between hypoglycemia in diabetic patients in the presence of comorbid conditions such as a history of cardiovascular diseases, stroke, renal disease, polycystic ovary syndrome, and cystic fibrosis.[4,10,13,19,26] In our study, the most common co-morbidity in patients with hypoglycemia was hypothyroidism (25.62%), followed by irregular menstruation (24.45%), anxiety disorder (18.46%), hypertension (12.77%), headache (10.93%), dizziness (3.93%) and asthma (3.86%). However, we did not observe a significant association between the presence of co-morbidity with hypoglycemia and the frequency of hypoglycemic episodes. Similar to the results by Yun et al., we did not observe a strong relationship between hypoglycemia in higher BMI patients with co-morbidities.[18]

The study has certain limitations. A smaller sample size and selection bias of the study cohort limits the generalizability of the study results. Further, data on fasting insulin was available only in a subset of the population, which might have affected the correlation between BMI and HOMA-IR. Hypoglycemia was considered only based on the OGTT values without taking clinical symptoms into account. We would like to emphasize the necessity of larger epidemiological studies to assess the risk factors associated with hypoglycemia in the general population.

In conclusion, we observed that increased BMI was associated with having HOMA-IR and high glucose levels at 0-30-60-120 minutes in OGTT. The occurrence of biochemical/reactive hypoglycemia during OGTT may be an indicator of early β-cell dysfunction and insulin resistance, suggesting the presence of underlying disease. Since biochemical hypoglycemia is linked to higher BMI due to poor diet and lifestyle habits, it is essential to identify these people in the initial phases through OGTT and intervene at the earliest to reduce the subsequent disease burden. Although hypoglycemia during the OGTT was not associated with BMI in this study, large-scale studies are needed to reveal this relationship.

Ethical Considerations: The study was approved by the local ethics committee (Reference No. 17.12.2020-40).

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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FERTILITY RATES OF SYRIAN MIGRANTS IN TURKEY, BABY BOOM, AND POSSIBLE FACTORS RELATED TO THEM

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Abstract

Objectives: Total fertility rate (TFR) is the average number of children born per woman of childbearing age. The baby boom refers to a noticeable increase in the birth rate and is believed to occur in migrants from war-torn and economically challenged countries. During the Syrian war in 2011, nearly 5 million Syrians had to leave their country. A significant part of the migration movement has been directed toward Turkey. In this study, it was aimed to investigate the baby boom presence of Syrian migrants in Turkey and to make comparisons.

Materials and Methods: Our study is an observational, descriptive epidemiological study, and the data were reviewed and compiled retrospectively. A comparison of TFRs of Turkey and Syria according to the last 20 years of the United Nations' data and the Turkey Demographic and Health Survey of 2018 was done.

Results: According to United Nations 2018 data, Turkey's TFR was 2.07, while Syria's was 2.8. According to 2018 Turkey's data, TFR in Syrian migrants is 5.3. When these rates are compared, it can be said that there is a significant increase in the fertility rate of Syrian migrants in Turkey, and this reveals the presence of a baby boom.

Conclusion: In conclusion, when TFRs in the pre-war period and after the war are compared in literature, there was a post-war baby boom in the Syrian migrant in Turkey. The factors which may have effect on the fertility of Syrian migrants found as psychological, economic, social, cultural, religious, and socio-demographic characteristics.

Keywords: Baby boom, total fertility rate, migration, migrant health, Syrian migrants.

Introduction

Many factors, such as wars, migrations, epidemics, and economic, medical, and technological developments throughout history, affect the world population data. Total fertility rate and crude birth rate are among the important public health issues and are universal rates used to determine population changes. These rates are used both to determine the population ratio of a country and are factors that determine the population development of countries. Total Fertility Rate (TFR) is one of the universal ratios used to determine population changes and refers to the average number of children born per woman of childbearing age (15-44 years). [1]

The baby boom refers to a noticeable increase in the birth rate, and it occurs in migrants from war-torn and economically challenged countries. The well-known baby boom is in the middle of the twentieth century, during the second world war, and after, and it is expressed in the relevant literature that it started in the early 1940s and ended in the 1960s.[2]

The fertility rate varies for different reasons in different parts of the world. Migration waves experienced after wars in many parts of the world appear as an undesirable phenomenon that became the main focus of this era. Migration mobility, which started with the history of humanity, is experiencing the most intense time today, after the Second World War. According to the United Nations High Commissioner for Refugees (UNHCR) 2019 data, there are 79.5 million forcibly displaced people in the world.[3] Migration, which affects society and individuals socially, culturally, and physically, also affects physical and mental health.[4] As a result of this, the migration waves around the world affect the fertility rate and perception, and thus the population.

Migration due to war, which is a social disaster, is itself a social disaster. Therefore, disaster ethics rules also apply to migration disasters. According to the "Justice" principle of disaster ethics, the right to receive services should be accessible to all immigrants, and instead of applying similar treatment to everyone as a requirement of fair treatment, it is important to offer different treatments as needed when appropriate.[5]

With the internal turmoil beginning in Syria in March 2011, nearly 7 million Syrians had to leave their country and migrate to other countries, especially Turkey, Lebanon, and Jordan. This migration wave, during which millions of Syrians had to leave their country, caused the largest migrant crisis in the world in a period exceeding a decade. Turkey has been implementing an "open door policy" toward Syrian migrants since the beginning. Turkey hosts the largest number of refugees (migrants) in the world in terms of its civilization, culture, and geographical location, expresses that it opens its doors to its neighbors as a symbol of humanity's conscience. Thus, Turkey, as an example of humanitarian diplomacy, states that it maintains its position as a country that takes the needy and asylum seekers under protection, as it has throughout its history.[6] A significant part of the migration movement turned towards Turkey, and Turkey is currently hosting 3.75

million Syrian migrants and giving them many rights.[3,7] One of the main ones is migrant health services. While health services were provided within the scope of Migrant Health Services in temporary accommodation centers, the scope of migrant health services increased over time due to the increase in the incoming population and the fact that it was distributed throughout Turkey. Strengthened Migrant Health Centers were established in settlements of over 20 thousand migrants. In addition, Community Mental Health Centers were established in order to eliminate the migration effects on individuals' mental health. Thus, within the scope of primary health care services, 773 Migrant Health Units serve in 182 migrant health centers in 29 provinces.[8]

The aim of this study is to determine the total fertility rate of Syrian migrant women living in Turkey in the light of current data, and to investigate whether the baby boom situation exists in Syrian migrants of Turkey and research and present possible causes that will affect the fertility rate.

Materials and Methods

Our study is an observational descriptive epidemiological research and the data were analyzed retrospectively. The total fertility rate(TFR) was used to investigate the baby boom presence of Syrian migrants in Turkey and to make comparisons. The TFR values of the countries were obtained from the most up-to-date sources of the United Nations (UN) and from the annually conducted official documents and studies in Turkey. First conducted in 1993 in Turkey, "*The Turkey Demographic and Health Survey (TDHS) is designed to provide data for monitoring the population and health status and to provide reliable estimates that can be used to evaluate and improve the current situation in fertility, family planning, maternal and child health.".*[10] In 2018, conducted by the Institute of Population Studies of Hacettepe University and supported by the Turkish Presidency's Strategy and Budget Department, the 2018 TDHS Syrian Migrant Sample includes demographic and health indicators collected for the first time for the Syrian migrant population in Turkey. [11] The 2018 TDHS, an internationally comparable study, was conducted worldwide within the framework of the models and standards of the Demographic and Health Surveys (DHS Program) project. Within the scope of the research, 2,216 Syrian migrant women aged 15-49 in 1,826 Syrian migrant households were interviewed in a country-wide sample.

TFR values between 2000 and 2020, which are accepted by national and international literature, were compared in 5-year periods and descriptive statistics were applied. In the descriptive statistics evaluated using the IBM SPSS Statistics 23 statistical package program, the numeric data were mean, median, standard deviation, and range of values; categorical data were expressed by descriptive methods such as ratio and percentage. In addition, descriptive statistics are presented in tables and graphs.

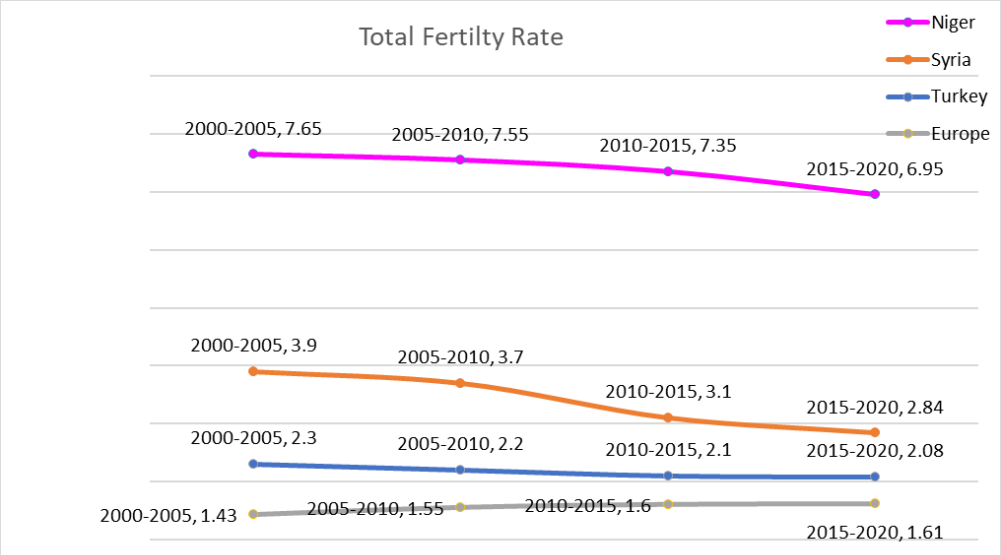
In addition to TFR, a literature review was conducted with the keywords "baby boom", "migration", "migrant health", Syrian migrants", and "total fertility rate" on the education rates of Syrian women, age at first marriage,

the total wanted fertility rate, contraception knowledge and usage rate in order to investigate the factors that may cause baby boom. The data of "The Turkey 2018 Demographic and Health Survey (TDHS) Syrian Migrant Sample", which is the most up-to-date and comprehensive study, were compared with the data in the literature.

Results

According to UN 2019 data, the total fertility rates of some countries in the last 20 years are listed in Figure 1 in 5-year periods.[9] Looking at the data, while Turkey's TFR in the last five years is 2.08, it is 2.84 for Syria and 1.61 for Europe. The majority of the countries with the highest fertility rates in the world between 2015 and 2020 are in Africa, and Niger is at the top of the list with a total fertility rate of 6.95.[9]

According to 2018 TDHS Syrian Migrant Sampling data, the TFR of Syrian migrant women living in Turkey is 5.3.[11] In comparison with the pre-civil war and post-war TFR of Turkey and Syria, which covers ten-year periods and is shown in Figure 2, a significant higher number is encountered in Syrian migrants living in Turkey. The Syrian TFR, which was 3.7 in the time period covering the years 2000-2010 before the 2011 Syrian civil war, tended to decrease between 2010-2020 after the war and was determined as 2.84.[9]



	2000-2005	2005-2010	2010-2015	2015-2020
Niger	7.65	7.55	7.35	6.95
Syria	3.9	3.7	3.1	2.84
Turkey	2.3	2.2	2.1	2.08
Europe	1.43	1.55	1.6	1.61

Figure 1. The trend of total fertility rates for some countries between 2000 and 2020, according to UN Data[9]

According to the TDHS 2018 report, the TFR of Syrian women in Turkey was found to be the highest, with 5.8 for women with no education or who did not complete primary school. This rate was found to be the lowest, at 4.1, among Syrian migrant women with a high school education or higher. The median age of first marriage for Syrian women aged 25-49 is 19.3 years. This value shows that half of the women in this age group got married before this age. The age of first marriage increased during the nearly twenty-year period following the 1990s. In the 2010s, that is, in the years when the civil war started, it is seen that the age of first marriage decreased again. The demand for family planning among married Syrian women between the ages of 15-49 is 64% in total. Of the Syrian migrant women who request family planning, 28% want to give birth after more time, and 36% want to terminate birth. Comparing the total wanted fertility rate (TWFR) with TFR is one way to determine the extent of undesirable fertility. The TWFR of Syrian migrant women with a TFR of 5.3 was found to be 4.2, which was calculated to be 21% less than the actual TFR, in other words, 1.1 children. The proportion of currently married Syrian migrant women between the ages of 15-49 who have knowledge of at least one family planning method is 99%. Despite this, the proportion of currently married Syrian women using any family planning method is only 43%. When the use of contraception methods is investigated, the withdrawal method is the most commonly used method, with 18%. The rate of using modern methods was 40% among Syrian migrant women who did not go to school or did not complete primary school and increased with education to 44% among women with high school or higher education. In the 2018 TDHS report, it was found that 9% of Syrian migrant women worked in a job, and 2% of them worked in the last year before the survey, although they were not actively working. While the highest rate of active work is 13% for Syrian women who have no children, this rate is 7% for Syrian women who have five or more children. [11]

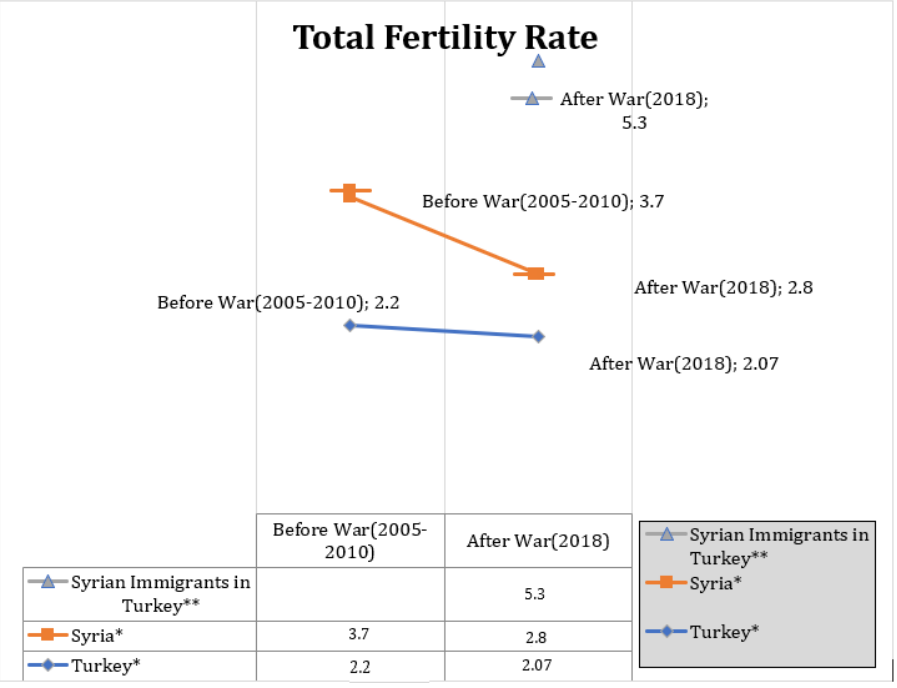


Figure 2. TFR between 2000-2005 and 2018 in Turkey and the Syria before the Syrian civil war and the total fertility rates in 2018 after the civil war

*According to UN Data, 5-year TFR between 2000-2005 in Turkey and the Syrian Arab Republic before the Syrian civil war[9] and the total fertility rates in 2018 after the Syrian civil war.[12]
** According to the 2018 TDHS data, the total fertility rate of Syrian migrants living in Turkey.[11]

Discussion

Due to the high fertility rate among migrated Syrians, similar to the "baby boom" observed in the world's population in world history, especially after the second world war, it can also apply to Syrian immigrants in Turkey since the beginning of the Syrian war.

When we investigated the causes of the baby boom in 1946-1960, it was generally associated with the increase in the welfare level by the post-war economic growth and giving postponed births in the future after the depression period. In addition to this, the underlying marital boom and marital fertility recovery also play a role. There is no consensus on the causes of the baby boom. Social scientists suggest that economic, social, and psychological factors together cause and affect this situation.[12] These include various factors such as socio-economic status, the structure of society, women's education level, age of first marriage, family planning services, accessibility of maternal and infant health services, women's age of menarche, knowledge, and use of contraception, religious beliefs, customs and traditions, society's and women's perspective on fertility, women's participation in the workforce, and government policies.[14–16]

Several hypotheses have been proposed about the relationship between migration and fertility. Among these, there are some prominent issues such as sociopathy, assimilation, adaptation, deterioration, and selectivity.[17] The effect of migration on the fertility rate may be based on the fertility behavior norms of the host countries or the fertility of the population left behind.

Social and demographic characteristics such as psychological, economic, social, cultural, and religious effects, women's education level, and age of first marriage may be effective in increasing the fertility rate of Syrian migrants in Turkey. A more detailed analysis of the possible reasons for the increase in the fertility rate of Syrian migrants living in Turkey is given below.

Education Level of Women

In some studies, there is an inverse relationship between women's education level and their fertility.[18,19] According to the TDHS 2018 report, the TFR of Syrian women in Turkey was found to be the highest with no education or who did not complete primary school. This rate was found to be the lowest among Syrian migrant women with a high school education or higher.[11] This point gives an important clue about the baby boom.

Age of First Marriage

There is a negative relationship between the age of first marriage and the total fertility rate. In addition, the "median age of first marriage" together with the "age of first marriage" of women are important indicators in

terms of risks that may be encountered during pregnancy.[19] According to the data, the age of first marriage increased during the nearly twenty-year period following the 1990s. [11] In the 2010s, that is, in the years when the civil war started, it is seen that the age of first marriage decreased again.[11] It can also be shown that the baby boom that took place after the second world war in world history caused an increase in postponed marriages and births during the war during the post-war welfare period.[2] Therefore, the young age of first marriage of Syrian migrants living in Turkey and the increase in marriage rates can be cited as a reason for the baby boom.

Access to Maternal and Child Health Services

According to the data published by the Directorate General of Migration Management of the Ministry of Interior of the Republic of Turkey, 70.8% of the Syrian migrants under temporary protection as of 25.11.2021 are women and children.[21] The accessibility and quality of maternal and child health and family planning services for this vulnerable group, of which Syrian migrants constitute the vast majority, has a positive effect on regulating the fertility of migrating women. Just as with the increasing welfare level after the second world war, this situation can sometimes pave the way for a baby boom. Although facilitating access to health services such as birthing units may be one of the factors that can cause a baby boom, access to health services cannot be restricted due to the principle of providing benefits in disaster ethics.

Along with the migration movement, which is closely related to public health, some new health policies need to be made and implemented.[22] As a matter of fact, "Women's Health Counseling Centers" specialized in maternal and child health, women's health, and psychosocial support were opened in order to increase the general quality of the health services scope for Syrian migrant women and to improve the access of women, young and disadvantaged groups to rights and services in Turkey. Within the scope of the "Project on Strengthening Access to Syrian and Other Migrant Women's Reproductive Health and Gender-Based Violence Services for Safe Spaces for Women and Girls and Women's Health Counseling Centers", a total of 30 Women's Health Counseling Centers started to work as a single center in 2015, currently serve Syrian migrant women in 17 provinces.[23]

With the Temporary Protection Regulation, which was published and entered into force by the Council of Ministers on 22.10.2014, "temporary protection status" was given to Syrian refugees registered in Turkey.[24] As defined in this regulation, the health services provided to Syrian refugees during their stay are provided free of charge at all care stages.[25]

In a speech by the president of Turkey, Recep Tayyip Erdogan, at the Global Refugee Forum held in Geneva in 2019, he stated that about 516 thousand Syrian babies were born in our country in the last eight years.[26] According to the "Syrian Women in Turkey" report in 2014, it is seen that 96% of pregnant women gave birth

in hospitals or clinics. [11] It is important for women to give birth in hospitals or clinics, both for their own health and for the health of newborn babies. The improvement in the health and living conditions of society has been effective in the baby boom in developing countries in the history of the world. Therefore, all health facilities for Syrian migrant women can be considered a positive factor that sets the stage for a baby boom.[27]

Family Planning, Knowledge and Use of Contraception

Of the Syrian migrant women who request family planning, 28% want to give birth after more time, and 36% want to terminate birth. The TWFR of Syrian migrant women was calculated to be 21% less than the actual TFR, in other words, 1.1 children.[11] As can be seen, the majority of people want to receive family planning services, and the rate of unwanted pregnancies is about one-third of it. This is important in terms of showing that the baby boom cannot be prevented at the desired level.

Another important factor affecting the fertility of women is the use of contraception. According to data from the TDHS 2018 report, the proportion of currently married Syrian migrant women between the ages of 15-49 who have knowledge of at least one family planning method is 99%. Despite this, the proportion of currently married Syrian women using any family planning method is only 43%. The rate of using modern methods increased with education among women in high school or higher education.[10] Additionally, according to 2017 data, the rate of using modern methods among women of reproductive age in the Syrian Arab Republic was over %60.[28]

Among the factors affecting the use of contraceptive methods in the world are ignorance, difficulty in accessing contraception methods, and traditional beliefs.[19] As can be seen, despite the knowledge of contraception, the lack of the desired frequency of use in Syrian migrant women stands out as an important risk factor for the baby boom compared with women in the Syrian Arab Republic. Qualitative studies with the relevant population are necessary in order to conduct an in-depth analysis of the situation(s) that caused this situation.

Religious Beliefs, Traditions and Customs, Perspective of Society and Women on Fertility

For many religions, being religious was found to be directly related to increased intention to have children.[29] This issue was also seen after the second world war. In addition, Syria is under the influence of middle eastern culture, Islamic religion, and traditional culture compared to the West, and the concept of fertility is seen as a positive phenomenon in the country.

As a result of a survey conducted with 50 Syrian migrant women in Turkey in 2015 on the factors affecting their fertility, when the reasons for giving birth are questioned, the most important of these factors are love, continuity of life, and the necessity of fertility for this. At the same time, in addition to these factors, other

factors were determined to be not getting divorced and staying with the husband, the man's reputation, the need for labor, and religious beliefs.[19] In addition, the participating women stated that not having children causes social pressure, which shows that they are also supported by them and that they continue the traditional structure. As a result, it shows that the fertility characteristics of Syrian refugee women are influenced by their close environment, community characters, traditional structure, and religious beliefs.[19] This suggests that an important component of the baby boom is also caused by cultural and existential factors.

In addition to these factors, it was observed in history that pronatalist policies regarding the need to prevent population decline during the second world war, especially in European countries, started in Germany and spread to various countries, including France and Belgium, and this situation was among the most effective causes of the baby boom.[1] It can be assumed that the Syrian migrant community adopts a pronatalist approach in order to balance their declining population during the war, and increasing the number of qualitative studies on this may be beneficial in understanding and managing this perception.

Women's Participation in the Workforce

An increase in women's participation in the workforce is associated with decreased fertility. Throughout the twentieth century, the lowest fertility rate in the world was observed in women with the highest education level, and there is a negative relationship between education level and fertility rate.[30] In the 2018 TDHS report, while the highest rate of active work is 13% for Syrian women who have no children, this rate is 7% for Syrian women who have five or more children.[11] In other words, the low numbers of women's participation in the workforce can be considered a factor in the baby boom.

The most important limitation of the study is that it is based on information from other studies. One of the limitations is that there is only one study on the demographic characteristics of Syrian immigrants in Turkey and that the sample and duration are not sufficient.

In conclusion, when the total fertility rates between 2005-2010 in the pre-war period and the total fertility rates in 2018 after the war were compared by international and national sources, this study showed that there was a post-war baby boom in the Syrian migrant population living in Turkey.

Moreover, relevant literature was reviewed on the possible causes of the baby boom, and these causes were found to be women's education level, age of first marriage, easy and free access to maternal and child health services, family planning, contraception knowledge, and use, religious beliefs, customs and traditions, society and women's perspective on fertility, and women's participation in the workforce. It is seen that the studies to be planned for the access of women, who are one of the vulnerable and risky groups in the migration process, to health services should be carried out by taking into account the significantly high total fertility rate among

Syrian migrant women and the possible factors that cause it. In light of the data found in this study, raising awareness about family planning and contraceptive methods, increasing the number and quality of Women's Health Counseling Centers for Syrian migrants living in Turkey, and providing language and educational support to Syrian refugee women are among the first steps to be taken against the baby boom.

In future studies, an in-depth and periodic investigation of the fertility perceptions of Syrian migrant women and the factors affecting them will be important in terms of improving the health services to be provided to them.

Ethical Considerations: Ethics committee approval (Document Date: 20/01/21, Document Number: E1-20-1437) was obtained from the local research ethics committee for the study.

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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THYROID CANCER IN ADOLESCENTS AND YOUNG ADULTS

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Abstract

Objectives: The incidence of thyroid cancer (TC) is increasing in adolescent and young adult (AYA) patients. Many types of cancer diagnosed in the AYA age group differ significantly in clinical and pathological features from cancers diagnosed in older age groups, but data on TC are limited. Our aim was to compare the clinicopathological features of TC in AYAs and adults ≥40 years old.

Materials and Methods: In total, 1013 patients with TC were retrospectively reviewed. Thyroid functions, ultrasonographic features of malignant nodules, cytological and histopathological findings, and recurrence and persistence rates were compared in AYAs and patients ≥40 years old.

Results: There were 229 (22.61%) AYA patients and 784 (77.39%) patients ≥40 age group. Of all cancer types, 93.12% in AYAs and 93.58% in the ≥40 age group were papillary thyroid cancer (PTC) (p=0.772). Multifocal thyroid tumors were detected in 62 (27.07%) of AYAs and 269 (34.31%) of the ≥40 age group (p=0.039). Incidental thyroid tumors were detected in 113 (37.05%) of AYAs and 583 (52.01%) of the ≥40 age group (p<0.01). The extrathyroidal extension (ETE) was detected in 9.61% of AYAs and 16.33% of patients ≥40 years old (p=0.012). Capsular and vascular invasion, lymph node metastasis, distant metastasis, persistence, and recurrence rates were similar.

Conclusion: There was no increase in the aggressive clinical and pathological features of TC in AYAs. ETE, multifocal tumors and incidental tumors were less common in AYAs than in patients ≥40 years old. PTC is the most common type in both groups, while the follicular variant PTC (FVPTC) subtype is increased in AYAs. Thyroid nodules should be carefully evaluated in AYAs, and diagnostic procedures should be recommended without delay. However, when TC is diagnosed in AYAs, the overtreatment potential of a disease with an excellent prognosis should also be considered.

Keywords: Adolescents and young adults; thyroid cancer, cytopathology, histopathology.

Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, and its overall incidence has increased significantly in the last 30 years.[1] Cancer in adolescents and young adults (AYAs) is defined by the National Cancer Institute (NCI) as diagnoses occurring among those aged 15 to 39 years.[2] TC is the most diagnosed cancer in AYA aged 20 to 29 years in both sexes, and most of the new cases are papillary thyroid cancers (PTC) that do not affect disease-specific mortality.[3] The incidence of TC in AYAs in the USA has increased exponentially in both women and men in the last two decades.[3] In addition, adolescents have an incidence of TC 10 times higher than young children, and it was shown that TC is five times more common in women than men during adolescence.[1] Although this increase in prevalence is often attributed to the increased use of imaging modalities and higher sensitivity of ultrasonography (US), there are also studies suggesting a true increase.[4] Still, data for AYAs are sparse. During the most recent ten years of available data, TC incidence rates rose rapidly in all AYA age groups, whereas mortality rates declined slightly by 0.5% annually. The 5-year relative survival rate for TC is generally high and exceeds 99% in AYA aged 20 to 39 years.[3]

Many types of cancer diagnosed in the AYA age group differ significantly from cancers diagnosed in other age groups in terms of risk factors, tumor biology, prognosis, and survival, but there are limited studies on TC in the literature. Previous studies have found that, although AYAs are more likely to be diagnosed with larger thyroid cancers or with locoregional lymph node involvement compared with older patients, they are less likely to be diagnosed with distant metastases and continue to have a better prognosis than their older counterparts.[5]

In this study, we aimed to compare clinical, ultrasonographical, cytological and histopathological features of TC in AYAs and patients ≥40 years old.

Materials and Methods

The medical records of patients who underwent thyroidectomy between December 2006 and September 2016 and were diagnosed with TC were retrospectively reviewed. The operation was performed based on the decision of a committee including endocrinology, general surgery, nuclear medicine, and pathology specialists. Patients with insufficient clinical data and histopathology reports, a second malignancy and unilateral resection, were excluded from the study. Local ethics committee approval was obtained in accordance with the ethical standards of the Helsinki Declaration.

Patients were subdivided into two age groups: 15-39 (AYAs) and ≥40 years old. Demographical and ultrasonographical features, cytological results and final histopathological diagnosis were obtained from medical records. Serum thyrotrophin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), antithyroid

peroxidase antibody (anti-TPOAb), and antithyroglobulin antibody (anti-TgAb) levels were measured by chemiluminescence methods (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA and UniCel DXI 800, Beckman Coulter, Brea, CA). The normal ranges for TSH, fT3, fT4, antiTPOAb, and anti-TgAb were 0.4–4 μIU/mL, 1.57–4.71 pg/ mL, 0.85–1.78 ng/dl, 0–35 IU/mL, and 0–40 IU/mL, respectively. The thyroid antibody level over the upper range of normal was evaluated as positive. The patients were classified as euthyroidism (both TSH and fT4 within normal limits), hypothyroidism (elevated TSH with low fT4), and hyperthyroidism (suppressed TSH with elevated fT4) according to preoperative thyroid functions.

Thyroid US was performed using an Esaote color Doppler US (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) with a superficial probe (Model LA523 13–4, 5.5–12.5 MHz). The localization, diameters, ratio of anterior-posterior to transverse diameter (AP/T), volume, echogenicity, texture, marginal regularity, presence of microcalcification and macrocalcification and peripheral halo of nodules were evaluated.

Before the fine needle aspiration (FNA) procedure, all patients were informed about the risks and possible complications related to the procedure, and their approval was obtained. FNA was carried out with a 27-gauge needle and 20-mL syringe under US guidance (Logic Pro 200 GE and 7.5 MHz probe, Kyunggigo, Korea) by experienced endocrinologists. All nodules >1 cm and nodules ≤1 cm with at least one suspicious US feature such as hypoechoic, irregular margins, absence of halo and presence of microcalcification were evaluated by FNA. Cytological findings were classified as non-diagnostic (ND), benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy and malignant according to Bethesda System.[6]

The type, size, multifocality and incidentality of the tumor, capsular invasion, vascular invasion, lymph node metastasis (LNM) and extrathyroidal extension (ETE) were recorded from histopathology reports. Malignant lesions were classified as PTC, follicular thyroid cancer (FTC), Hurthle cell cancer (HCC), well-differentiated tumor of uncertain malignant potential (WDT-UMP), medullary thyroid cancer (MTC) and anaplastic thyroid cancer. Histological variants of PTC were further grouped as classical, follicular, oncocytic, tall cell, and others (encapsulated, solid/trabecular, diffuse sclerosing, columnar cell, warthin-like).

All statistical analyzes were performed with a software package program (SPSS, version 11.5 for Windows; SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was tested with Kolmogorov–Smirnov test. Descriptive statistics were presented as mean ± SD, with medians minimum–maximum) for continuous variables and percentages (%) for categorical variables. The differences in groups were compared by the student's t-test for parametric variables and the Mann–Whitney U test for

nonparametric variables. The chi-square test was used to investigate the difference between the groups regarding the categorical variables. A value of $p<0.05$ was considered to indicate statistical significance.

Results

The data of 1013 patients who were diagnosed with TC histopathologically were analyzed. 229 (22.61%) patients were in the AYA group (15-39), and 784 (77.39%) were in the ≥ 40 age group. There were 187 (81.66%) female and 42 (18.34%) male patients in the AYA group (Table 1). In the ≥40 age group, there were 602 (76.79%) females and 182 (23.21%) males. There was not any significant difference in sex distribution between groups (p=0.117). The mean age was 32.03±4.95 and 54.54±9.24 years in AYAs and ≥40 age groups, respectively (p< 0.001). Serum TSH, fT3, fT4 and anti-TPO and anti-Tg antibody positivity at the time of diagnosis were similar in both groups (p=0.094, p=0.253, p=0.857, p=0.626 and p=0.871, respectively). Family history of thyroid cancer and radiation history to the head and neck region were similar in both groups (p=0.969 and p=0.657, respectively). Preoperative ultrasonography features, operation indications and surgical approach were similar in AYAs and in the ≥40 age group (Table 1).

Cytological and histopathological features in AYAs and ≥40 age patients are compared in Table 2**.** There were a total of 1426 malignant foci, 305 (21.39%) were in AYAs, and 1121 (78.61%) were in the ≥40 age group. 62 (27.07%) of AYAs and 269 (34.31%) of ≥40 age group had multifocal TC (p=0.039). LNM, capsular invasion, vascular invasion, lymphatic invasion, and distant metastasis rates were similar in both groups (p=0.246, p=0.848, p=0.134, p=0.752 and p=0.889, respectively) (Table 2). ETE was detected in 22 (9.61%) of the tumors of the AYAs and in 128 (16.33%) of the tumors of patients ≥40 years old (p=0.012). Distant metastases were observed in a total of 5 patients in the study population. Lung metastases were observed in 1 patient in AYAs. In the ≥40 age group, two patients had lung metastases, 1 had vertebral bone metastases, and 1 had pelvic bone metastases with lung.

Histopathological features of malignant nodules are compared in Table 3. Tumor diameter was 10.14±11.54 mm in the AYAs, and 11.52±15.56 mm (p=0.184) in the ≥40 age group 198 (64.92%) and 719 (64.14%) tumor foci were microcarcinoma in AYAs and ≥40 age group, respectively (p=0.801). While 113 (37.05%) of tumors in AYAs were incidental, 583 (52.01%) tumors in the ≥40 age group were incidental (p<0.001).

The histopathological tumor type distribution was similar in both groups. 284 (93.12%) of tumors in AYAs and 1049 (93.58%) of tumors in patients ≥40 years old were PTC (p=0.772). Classical variant PTC was significantly higher in the ≥40 age group, while follicular variant PTC (FVPTC) was significantly higher in AYAs (p=0.005 and p=0.003, respectively). Oncocytic and tall cell variant PTC were similar in both groups (p=0.333 and p=0.653, respectively).

Table 1. Clinical and ultrasonographical features of adolescent and young adult patients and ≥40 age patients with thyroid cancer

	AYA patients (15-39) n (%) 229 (22.61)	**≥40 age patients n (%) 784 (77.39)**	**P***
Age	32.03±4.95	54.54±9.24	**<0.001**
Sex Female Male	 187 (81.66) 42 (18.34)	 602 (76.79) 182 (23.21)	 0.117
Family history of thyroid cancer (n/%)	4 (1.75)	14 (1.79)	0.969
Radiation history to the head and neck region (n/%)	1 (0.44)	2 (0.26)	0.657
TSH (μIU/mL)	1.66 ±2.14	1.63± 1.65	0.094
fT4 (ng/dL)	1.17±0.36	1.16 ±0.31	0.857
fT3 ((pg/mL)	3.27±2.03	3.24±0.87	0.253
Anti-TPO positivity (n =202)	48 (26.66)	154 (23.91)	0.626
Anti-Tg positivity (n = 201)	46 (25.32)	155 (24.54)	0.871
Functional status Euthyroid Hypothyroid Hyperthyroid	 177 (77.29) 19 (8.30) 33 (14.41)	 566 (72.20) 64 (8.16) 154 (19.64)	 0.196
Nodule number in ultrasonography	3.08± 2.69	4.66± 3.41	**<0.001**
Ultrasonography features of malignant nodule			
Anteroposterior diameter (mm) Transverse diameter (mm) Longitudinal diameter (mm)	10.91 (4.53-43.12) 12.1 (5.33–68.28) 16.2 (4.24–92.32)	11.7 (4.24-41.1) 12.5 (3.46–92.32) 17.5 (3.9–94.21)	0.142 0.134 0.112
AP/T	0.87± 0.23	0.89 ± 0.25	0.512
Volume (cm3)	0.98 (0.04–118.61)	0.94 (0.03–223.43)	0.081
Localization Right Left Isthmus	 128 (55.90) 97 (42.36) 4 (1.74)	 430 (54.85) 339 (43.24) 15 (1.91)	 0.954
Texture Solid Cystic/mixed	 221 (96.51) 8 (3.49)	 756 (96.43) 28 (3.57)	 0.955
Echogenicity Isoechoic Hypoechoic Iso-hypoechoic	 86 (37.55) 53 (23.14) 90 (39.31)	 296 (37.76) 178 (22.70) 310 (39.54)	 0.990
Microcalcification	92 (40.17)	328 (41.84)	0.653
Macrocalcification	78 (34.06)	278 (35.46)	0.697
Hypoechoic halo	47 (20.52)	144 (18.37)	0.463
Irregular margins	137 (59.83)	454 (57.91)	0.605
Surgical approach BTT/NT Hemithyroidectomy	 226 (98.69) 3 (1.31)	 774 (98.72) 10 (1.28)	 0.967

Operation indications			
Giant nodule	37 (16.16)	142 (18.11)	
Hyperthyroidism	16 (6.99)	68 (8.67)	
Cytology			
Malignant	37 (16.16)	137 (17.47)	
Suspicious for malignancy	36 (15.72)	100 (12.76)	
FN/SFN	16 (6.99)	40 (5.10)	0.458
AUS/FLUS and suspicious ultrasonography features	40 (17.47)	156 (19.90)	
Non-diagnostic	23 (10.04)	73 (9.31)	
Parathyroid pathology	1 (0.43)	26 (3.32)	
Other	23 (10.04)	42 (5.36)	

(TSH: thyrotropin, fT3: free triiodothyronine, fT4: free thyroxine, anti-TPO: antithyroid peroxidase antibodies, anti-Tg: antithyroglobulin antibodies, US: ultrasonography, AP/T: ratio of anterior-posterior to transverse diameter, BTT/NT: bilateral total thyroidectomy/near-total thyroidectomy, FN/FNS: follicular neoplasm/suspicious for follicular neoplasm, AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance)
*Significant p values are indicated as bold in the table

The mean follow-up period was similar in the two groups (p=0.876) (Table 4). Radioactive iodine (RAI) ablation was performed in 183 (79.91%) of AYAs and 630 (80.36%) of the ≥40 age group (p=0.882). Seventy-three (39.89%) AYAs and 263 (41.75%) ≥40 age group were ablated with an RAI dose greater than 100 mCi. Persistence and recurrence rates were similar in the two groups (p=0.499 and p=0.407, respectively). The mean time of recurrence was 28.43±16.42 months in AYAs and 22.54±4.43 months in the ≥40 age group (p=0.438).

Table 2. Cytological and histopathological features of adolescent and young adult patients and ≥40 age patients with thyroid cancer

	AYA patients (15-39) n (%) 229 (22.61)	**≥40 age patients n (%) 784 (77.39)**	**P***
Cytological diagnosis			
Non-diagnostic	23 (10.04)	73 (9.31)	0.739
Benign	77 (33.62)	278 (35.46)	0.608
AUS/FLUS	40 (17.47)	156 (19.90)	0.413
FN/SFN	16 (6.99)	40 (5.10)	0.272
Suspicious for malignancy	36 (15.72)	100 (12.76)	0.247
Malignant	37 (16.16)	137 (17.47)	0.642
Total tumor foci	305 (21.39)	1121 (78.61)	
Tumor number per patient	1.52±1.23	1.57±1.12	0.064
Multifocality	62 (27.07)	269 (34.31)	**0.039**
Lymph node metastasis	21 (9.17)	58 (7.40)	0.246
Capsular invasion	68 (29.69)	238 (30.36)	0.848
Vascular invasion	10 (4.37)	56 (7.14)	0.134
Extrathyroidal extension	22 (9.61)	128 (16.33)	**0.012**
Lymphatic invasion	5 (2.18)	20 (2.56)	0.752
Distant metastases	1 (0.44)	4 (0.51)	0.889

(AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance, FN/SFN: follicular neoplasm/suspicious for follicular neoplasm, PTC: papillary thyroid cancer, WDT-UMP: well-differentiated tumor of uncertain malignant potential)
*Significant p values are indicated as bold in the table

Table 3. Histopathological features of malignant thyroid nodules in adolescent and young adult patients and ≥40 age patients

	AYA patients (15-39) n (%) 305 (21.39)	**≥40 age patients n (%) 1121 (78.61)**	**P***
Tumor diameter	10.14 ± 11.54	11.52 ± 15.56	0.184
Microcarcinoma	198 (64.92)	719 (64.14)	0.801
Incidentality	113 (37.05)	583 (52.01)	**<0.001**
Tumor type			
Papillary	284 (93.12)	1049 (93.58)	0.772
Follicular	8 (2.62)	23 (2.05)	0.544
Hurthle cell	4 (1.31)	17 (1.51)	0.792
Medullary	3 (0.98)	12 (1.07)	0.895
Anaplastic	1 (0.33)	4 (0.36)	0.940
WDT-UMP	5 (1.64)	16 (1.43)	0.785
PTC variants	n=273	n=1016	
Classical	206 (75.46)	842 (82.87)	**0.005**
Follicular	52 (19.05)	123 (12.11)	**0.003**
Oncocytic	8 (2.93)	20 (1.97)	0.333
Tall cell	4 (1.46)	19 (1.87)	0.653
Other	3 (1.10)	12 (1.18)	0.910

(PTC: papillary thyroid cancer, WDT-UMP: well-differentiated tumor of uncertain malignant potential)
*Significant p values are indicated as bold in the table

Table 4. Follow-up data of adolescent and young adult patients and ≥40 age patients with thyroid cancer

	AYA patients (15-39) n (%) 229 (22.61)	**≥40 age patients n (%) 784 (77.39)**	**P***
Follow-up period (month)	40.42 ± 22.78	39.56 ± 14.12	0.876
RAI treatment	183 (79.91)	630 (80.36)	0.882
RAI dose (mCi)			
≤100	110 (60.11)	367 (58.25)	0.654
>100	73 (39.89)	263 (41.75)	
Persistence	5 (2.18)	12 (1.53)	0.499
Recurrence	1 (0.44)	7 (0.89)	0.407
Recurrence time (months)	28.43 ± 16.42	22.54 ± 4.43	0.438

(RAI: radioactive iodine)
Significant p values are indicated as bold in the table

Discussion

Many types of cancer diagnosed in the AYA age group differ significantly from cancers diagnosed in other age groups in terms of clinical and histopathological features, but information on TC is limited. In our study, we did not observe an increase in aggressive clinical and pathological features of TC in AYAs. There was no difference

in LNM, capsular and vascular invasion in AYAs, and ETE was less common. Multifocal tumors and incidental tumors were less common in AYAs than in patients ≥40 years old. While PTC was the most common type in both groups, the FVPTC subtype was increased in AYAs.

In recent years TC has become one of the most common cancers in the AYA population.[1] This increase in the incidence of TC can be attributed to various risk factors such as overdiagnosis. Excessive iodine intake, diagnostic radiation and environmental exposure are some other causes blamed for this increase. The major risk factor for the development of PTC is radiation exposure to the head and neck region, especially during childhood and adolescence.[7] Most cases of radiation-induced PTC are due to therapeutic radiation administered to treat a previous malignancy.[8] The onset period is usually between 10 and 20 years after exposure to radiation. Exposure to major environmental RAI from the Chernobyl nuclear accident in 1986 is another risk for the development of PTC, especially in children and adolescents.[9] In previous studies, the clinical behavior of radiation-induced TC does not appear to differ significantly from sporadic tumors.[10] In our series, the history of radiation to the head and neck region in AYA patients was similar to the ≥40 age group. We did not find any difference between the groups in terms of family history of thyroid cancer. In addition, the role of iodine in the pathogenesis of TC is controversial. Dietary iodine deficiency is associated with FTC, while excess iodine increases the risk of PTC.[11] In our study, while more than 90% of AYAs had PTC, a small number of FTC were detected, and no trend towards FTC was observed in AYAs. Accordingly, our country seems to have turned from iodine deficiency to excessive iodine intake.

The pathological classification and histological criteria of DTCs in AYAs are the same as in adults. While PTC accounts for more than 90% of cases in the AYA population,[3] FTC is rare. Low-risk subtypes (classic and follicular variants) of PTC remain the most common. Solid/trabecular and diffuse sclerosing subtypes of PTC are considered high-risk in adults[12,13] but are unclear in AYAs. In accordance with the literature, in our study, more than 90% of AYAs had PTC, and a small number of FTC were detected. MTC, poorly differentiated tumors, and anaplastic TC are rarer in younger patients. MTC accounts for approximately 5% of all thyroid malignancies, and the mean age at diagnosis is 50 years. Only about one-third of MTC cases occur in patients younger than 40 years old.[14] In our study, we did not find any difference in the rate of MTC and anaplastic thyroid carcinoma between AYAs and patients ≥40 years old.

Several clinicopathological features, such as age, gender, tumor size, ETE, LNM and distant metastasis, are well-known prognostic factors in PTC patients.[15] ETE is defined as the spread of the tumor beyond the thyroid capsule to adjacent soft tissue. It is generally accepted that advanced ETE adversely affects the results of PTC. Previous studies have shown that tumor size and older age are independent risk factors for ETE, and patients with ETE are more likely to have positive surgical margins.[16] That is, sustained tumor growth will increase the likelihood of the tumor extension beyond the thyroid capsule, especially in peripheral tumors. Aging restrains

adaptive immunity and makes the tumor microenvironment more immunosuppressive, which may facilitate the invasion process.[17] In our study, ETE was more common in patients ≥40 years old than in the AYAs.

The relationship between age and multifocality is not clear. In some studies, no significant relationship was found between increasing age and multifocality,[18] while in others, an increased risk of multifocality was reported in patients >45 years old.[19] In our study, multifocal TC was significantly higher in the ≥40 years old patients than in the AYAs. Previous studies showed a significant correlation between LNM, ETE and tumor size and multifocality, suggesting that multifocality is an indicator of disease progression. Multifocality has also been shown to be associated with an increased risk of disease recurrence.[20]

The increase in incidental TC (ITC) is one of the most important factors responsible for the increase in the incidence of total cancer. There are controversial findings with regard to ITC rates in different age populations. Although some previous studies have reported no change in rates of ITC according to age,[21] some have reported that it is more prevalent in older ages.[22] In our study, ITC was detected more frequently at older ages. A possible reason for this finding may be the increase in the frequency of admission to the hospital for different reasons as the age increases and the increase in the use of imaging studies that are responsible for the detection of incidental thyroid lesions. In addition, elderly patients with an incidental thyroid lesion may be subject to more aggressive diagnostic follow-up than younger individuals, which may lead to an increased incidence of ITC in these patients.

Although pediatric and AYA patients more commonly present with local extension, cervical node involvement, and pulmonary metastases, there is an excellent overall survival rate (>95%) 30 years after treatment.[23] This likely reflects the underlying tumor biological differences between pediatric/adolescent and adult patients. Some tumor subtypes, such as FVPTC and diffuse sclerosing variants of PTC, are more common in children and young adults than in older individuals.[24] FVPTC is the second most common PTC variant and is characterized by follicular growth pattern and cytological features of papillary carcinoma.[25] Similarly, in our study, FVPTC was significantly higher in the AYAs than in the ≥40 age group.

Most AYAs diagnosed with TC are treated according to the approaches used in adult patients. However, increasing evidence suggests that AYAs are molecularly different from other age groups and have a higher risk of long-term and late effects, including infertility, sexual dysfunction, cardiovascular disease, and future cancers, compared with older patients. Since children and adolescents with PTC are more likely to have cervical lymph node and pulmonary metastases, an aggressive treatment approach is often followed, which includes total thyroidectomy followed by radioiodine residual ablation.[26] Given the high overall survival rate, the complications and acute, subacute, and delayed toxicities of the chosen therapy should be carefully considered.

Despite an excellent overall prognosis for AYAs with DTC, there are many challenges that affect disease morbidity. First, AYAs are more likely to have no health insurance than older patients, and this age group is more likely to experience delays in cancer diagnosis due to the lack of cost-effective early detection methods. The risks of surgical complications are closely related to the age of the patient, the extent of the disease, and the experience of the surgeon. Although these relationships are well known, some of the young patients continue to have thyroid surgery in centers with insufficient thyroidectomy experience. In particular, the associated risks of thyroidectomy, including recurrent laryngeal nerve palsy, hypoparathyroidism, and the need for lifelong thyroid hormone replacement, are more devastating for the AYA population. In addition to surgical complications, there are several reports suggesting an increased risk of non-thyroid, secondary malignancies in patients receiving RAI compared to those not receiving RAI.[27] Therefore, although DTC is a disease with low disease-specific mortality, it can progress with short and long-term complications.

RAI therapy is used following thyroid surgery to prevent disease recurrence and to treat persistent or metastatic TC.[28] The increasing diagnosis of TC in recent years and the frequent occurrence of AYAs with metastatic disease may be a factor that increases the use of RAI in this population. The toxicities associated with RAI therapy are dose-related. RAI may cause temporary gonadal dysfunction, but subsequent infertility is rare except after high doses.[28] In addition, an increased risk of secondary malignancy has been reported after RAI treatment for TC.[29] Although serious adverse events are rare and possibly due to cumulative and higher doses of RAI treatment, they may be of particular concern for AYAs.

There are some limitations in our study. Firstly, it is a retrospective and single-center study. Secondly, central lymph node dissection is not routinely performed in patients who underwent thyroidectomy in our center, and this may have confused the nodal status of the patients. However, prophylactic central lymph node dissection is still controversial, and there is no definite recommendation in favor of this procedure.[30] In addition, the inability to perform molecular tests in our center during our study is another limitation. Lastly, the mean follow-up time in our study was relatively low, which might have caused low recurrence rates in our series.

In conclusion, we did not observe an increase in the aggressive clinical and pathological features of TC in AYAs. US and cytopathological features of malignant nodules in AYAs seem to be mostly identical with ≥40 years old patients. LNM, capsular and vascular invasion do not differ, and ETE is less common in AYAs. FVPTC subtype is increased in AYAs. Multifocal and incidental tumors are less common in AYAs. The incidence of TC is increasing rapidly in AYAs, and it is important for primary care physicians to refer patients to an endocrinology specialist for the diagnosis of thyroid nodules detected in AYAs and regular follow-up of patients with TC. Thyroid nodules in AYAs should be evaluated carefully, and diagnostic procedures should be offered without delay. On the other hand, the potential for overtreatment of a disease with an excellent prognosis, regardless of stage, should be considered when TC is diagnosed in AYAs.

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Ethical Considerations: The present study was approved by the ethics committee of Ankara City Hospital (REC number: E1-21-2082, Date:20.10.2021).

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EXPLORING ELECTROPHYSIOLOGY STUDENTS' LEARNING STYLES AND ATTITUDES TOWARD ONLINE LEARNING

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Abstract

Objectives: A learning style can be described as an individual difference in perceiving and processing information in one's mind. The previous research suggested that one may attain greater achievement when teaching is organized according to their learning style. Moreover, upon comparing online and traditional learning environments, learning styles may also need to be considered in distance education. The present study aimed to explore the attitudes of electrophysiology students toward online learning by their learning styles.

Materials and Methods: This cross-sectional study recruited 101 students, 20.79% (n=21) males and 79.21% (n=80) females, enrolled in the electrophysiology program in the 2021-2022 academic year. The data were collected using a demographic information form, the VARK Learning Styles Questionnaire, and the Online Learning Attitude Scale (OLAS).

Results: Almost all participants (93.07%; n=94) attended distance education during the pandemic. The findings revealed that the participants mostly adopted all of the Visual-Auditory-Read/Write-Kinesthetic (39.60%; n=40) learning styles, while kinesthetic learning style was adopted the most (13.86%; n=14) as a unimodal learning style. Besides, while having a high attitude toward online learning, the students scored the highest on the OLAS APPEFF subscale (3.54±1.02). Finally, it was concluded that the students with bimodal and quadrimodal learning styles had significantly higher attitudes toward online learning than those adopting a unimodal learning style (p=0.034 and 0.011, respectively).

Conclusion: Overall, the participating electrophysiology students had high attitudes toward online learning and often adopted a multimodal learning style.

Keywords: Learning styles, student attitudes towards online learning, distance learning, electrophysiology.

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Introduction

The COVID-19 pandemic-led crisis mandated higher education institutions to switch to other learning modes, particularly distance education. However, the relevant research suggested that a significant part of the academic world was totally unprepared to satisfy students' educational demands during the pandemic. Traditional and online education platforms bear diverse structures, contexts, requirements, and demands.[1] In previous findings, learning styles were shown as an essential factor in setting distance learning environments.[2, 3] Beadles et al. investigated students' tendency to choose web-based degree programs based on their learning styles and found that learning styles may influence the choice of educational approach, that students choosing to enroll in traditional and web-based programs significantly differed learning styles, and that intuitive students might be more likely to favor web-based programs.[3] Moreover, studies comparing the effects of online and traditional learning environments on student achievement concluded that learning style is effective in distance education. The previous research also suggested that one may attain greater motivation and academic achievement when teaching is organized according to their learning styles.[2, 4] In addition, success in online learning can be directly associated with the learner's attitudes and approaches toward such environments. In this sense, it can be proposed that learners with adverse attitudes toward online learning environments may have poor adaptation and achievement.[5] Therefore, it seems valuable to uncover distance learners' attitudes toward distance learning. However, to the best of our knowledge, the literature hosts no studies investigating electrophysiology students' learning styles and attitudes toward online learning. Thus, the present study attempted to uncover electrophysiology students' learning styles and attitudes toward online learning and to evaluate their attitudes by their learning styles. The findings are thought to contribute to generating novel strategies in electrophysiology programs to enhance teaching methods for theoretical and applied curricula.

Materials and Methods

Sample

The sample consisted of first and second-year students enrolled in an electrophysiology associate degree program in the 2021-2022 academic year and attending distance and/or face-to-face education. The sample was conveniently selected based on voluntary participation. Moreover, the sample size covered almost the entire number of students in both years of study (excluding those rejecting to answer the survey questions)

Data Collection

In line with the purpose of the study, a demographic information form was used to collect the students' demographic characteristics (gender, age, year of study, attendance in distance education during the pandemic,

and tools used in distance education). While their learning styles were assessed using the VARK Learning Styles Questionnaire (VARK-LSQ), and their attitudes toward online learning were evaluated using the Online Learning Attitude Scale (OLAS). Finally, the students' grade point averages (GPA) were obtained from their end-of-year transcripts.

VARK Learning Styles Questionnaire (VARK-LSQ)

The questions in the VARK-LSQ are aimed at uncovering how one exchanges information and which perceptual and sensory characteristics govern their learning or teaching preferences.[6] Sixteen questions in the instrument offer 16 different scenarios and ask respondents what they would do in such scenarios. One's learning style is measured in four different groups according to the method proposed by Fleming: visual, auditory, read/write, and kinesthetic. Yet, it should be noted that one may adopt one, more, or all of these four different learning styles, implying multimodal learning style preferences.[7] Düzgün carried out the validity and reliability study of the VARK-LSQ in the Turkish context.[8] While he calculated the internal consistency coefficient for the total VARK-LSQ score to be 0.76, it was found to be 0.85 in this study.

Online Learning Attitude Scale (OLAS)

OLAS was developed by Usta, Uysal, and Okur (2016).[5] The 20-item instrument is scored on a 5-point Likert-type scale ranging from 5 (True at all) to 1 (Not at all true). The reliability analysis of the scale was replicated in this study, and the internal consistency coefficient was found to be 0.94 for the total score, 0.68 for the general acceptance subscale (GENACP), 0.94 for the individual awareness subscale (INDAWR), 0.86 for the usefulness subscale (USEFUL), and 0.69 for the application efficiency subscale (APPEFF). Moreover, the confirmatory factor analysis (CFA) resulted in the following fit indices: $\chi^2/df = 1.55$, RMSEA = 0.07, CFI = 0.98, PNFI = 0.82, NNFI = 0.98, and SRMR = 0.05.

Ethical Considerations

The Ethics Committee of Health Sciences University granted ethical approval to this study (2022-113 dated 04.21.2022). All research procedures were executed in accordance with the principles of the revised Declaration of Helsinki. Besides, relevant permissions were obtained from the school director to carry out this study and from the authors via e-mail to utilize their instruments in this research.

Statistical Analysis

Descriptive statistics for continuous variables are shown as mean ± standard deviation, minimum, and maximum values, while they are presented as percentages and numbers for categorical variables. The

Kolmogorov-Smirnov test, tables, and histograms were resorted to check the normality of distribution. Accordingly, pair-wise comparisons of the normally distributed data were performed using an independent samples *t*-test. However, the Mann Whitney-U and Kruskal-Wallis H tests were utilized in the analysis of learning styles since the group distribution for this variable was less than 30 participants. Moreover, the linear relationships between the relevant variables were sought using Pearson's correlation analysis. All statistical analyses were performed on the IBM SPSS 26.0 and LISREL 8.80 software, and a *p*-value <0.05 was considered statistically significant.

Results

Participants' characteristics

There were 21 (20.79%) male and 80 (79.21%) female participants in the study. While 47.52% (n=48) were first-year students, 52.48% (n=53) were second-year students. Almost all participants (93.07%; n=94) attended distance education during the pandemic. While 67.02% (n=63) of the participants used their personal computers in distance education, 56.38% (n=53) attended online classes with their smartphones (Table 1). The mean GPA of the students was found to be 3.22±0.33 (2.28-3.72).

Table 1. Tools used during distance education.

		n	**%**
Attendance in distance education during the pandemic	Yes	94	93.07
	No	7	6.93
	Total	101	100.00
Personal computer	Yes	63	67.02
	No	31	33.98
	Total	94	100.00
Smartphone	Yes	53	56.38
	No	41	43.62
	Total	94	100.00
Tablet	Yes	10	10.64
	No	84	89.36
	Total	94	100.00

Participants' learning styles

Considering the distribution of learning styles, 39.60% (n=40) of the students adopted all of the visual-auditory-read/write-kinesthetic learning styles, and 13.86% (n=14) of those adopting a unimodal learning style preferred the kinesthetic learning style (Table 2). When grouping learning styles by the number of

preferences, it was found that the majority of the students (39.60%; n=40) were quadrimodal and that the trimodal style was the least adopted one (13.86%; n=14; Table 3). Finally, while most participants (70.30%) preferred the multimodal learning style, 29.70% were unimodal learners.

Table 2. Distribution of the participants' learning styles (n = 101)

Learning Style	***n***	**%**
V	4	3.96
A	7	6.93
R	5	4.95
K	14	13.86
VA	1	0.99
VK	1	0.99
VR	2	1.98
AK	5	4.95
AR	5	4.95
RK	3	2.97
VAK	2	1.98
VRK	4	3.96
ARK	8	7.92
VARK	40	39.60

(V: Visual, A: Auditory, R: Read/Write, K: Kinesthetic, VA: Visual-Auditory, VK: Visual-Kinesthetic, VR: Visual-Read/Write, AK: Auditory-Kinesthetic, AR: Auditory-Read/Write, RK: Read/Write-Kinesthetic, VAK: Visual-Auditory-Kinesthetic, VRK: Visual-Read/Write-Kinesthetic, ARK: Auditory-Read/Write-Kinesthetic, VARK: Visual-Auditory-Read/Write-Kinesthetic.)

Table 3. Distribution of the participants by learning style groups (n = 101).

Group	**Preference**	***n***	**%**
Unimodal	V-A-R-K	30	29.70
Bimodal	VA-VK-VR-AK-AR-RK	17	16.83
Trimodal	VAK-VRK-ARK	14	13.86
Quadrimodal	VARK	40	39.60

(V: Visual, A: Auditory, R: Read/Write, K: Kinesthetic, VA: Visual-Auditory, VK: Visual-Kinesthetic, VR: Visual-Read/Write, AK: Auditory-Kinesthetic, AR: Auditory-Read/Write, RK: Read/Write-Kinesthetic, VAK: Visual-Auditory-Kinesthetic, VRK: Visual-Read/Write-Kinesthetic, ARK: Auditory-Read/Write-Kinesthetic, VARK: Visual-Auditory-Read/Write-Kinesthetic.)

Participants' attitudes toward online learning

When it comes to attitudes toward online learning, it was discovered that the participants scored the highest and the lowest on the APPEFF subscale (M=3.54, SD=1.02) and INDAWR subscale (M=2.48, SD=1.36). Besides, the students were found to have high total OLAS scores (M=3.50, SD=0.87) (Table 4).

The findings revealed no significant differences between the students' attitudes toward online learning by year of study. It was also the case regarding the total OLAS score by gender, but the male participants had significantly higher scores on the usefulness subscale than their female counterparts (p=0.037) (Table 5). Moreover, it was concluded that the bimodal and quadrimodal learners had significantly higher attitudes toward online learning than the unimodal participants (p=0.034 and 0.011, respectively) (Table 6). Finally, there was no significant association between the students' attitudes toward online learning and their GPAs.

Table 4. The participants' attitudes toward online learning (n = 101).

Subscale	***M***	***SD***
GENACP	3.40	1.02
INDAWR	2.48	1.36
USEFUL	3.28	1.25
APPEFF	3.54	1.02
Total Score	3.50	0.87

(SD: Standard deviation, M: Mean, GENACP: General Acceptance, INDAWR: Individual Awareness, USEFUL: Usefulness, APPEFF: Application Efficiency.)

Table 5. The participants' attitudes toward online learning by gender (n = 101).

Subscale	**Gender**	***n***	***M***	***SD***	**p***
GENACP	Male	21	3.50	1.27	-
	Female	80	3.37	0.94	
INDAWR	Male	21	3.02	1.43	-
	Female	80	2.33	1.31	
USEFUL	Male	21	3.45	1.54	0.037
	Female	80	3.24	1.17	
APPEFF	Male	21	3.60	1.21	-
	Female	80	3.53	0.98	
Total Score	Male	21	3.50	1.06	-
	Female	80	3.50	0.82	

* Independent samples *t*-test; a *p*-value < 0.05 was accepted as significant.
(SD: Standard deviation, M: Mean, GENACP: General Acceptance, INDAWR: Individual Awareness, USEFUL: Usefulness, APPEFF: Application Efficiency.)

Table 6. The relationship between the participants' learning style preferences and their attitudes toward online learning (n = 101)

Group	*n*	Mean Rank	Sum of Ranks	*U*	*p**
1-Unimodal	30	28.50	855.00	390.000	0.011
4-Quadrimodal	40	40.75	1630.00		
1-Unimodal	30	20.88	626.50	161.500	0.034
2-Bimodal	17	29.50	501.50		

*Mann Whitney-U test; a *p*-value < 0.05 was accepted as significant.

Discussion

A learning style is often defined as one's distinctive and consistent approaches to perceiving, processing, organizing, and interpreting information.[9] The VARK-LSQ, developed by Fleming and Mills, is also widely adopted thanks to its ease of administration, robust validity, and enhanced learning materials and can also be adapted to healthcare settings. [10-12]

Visual (V) learners learn best from the information presented through images (e.g., pictures, illustrations, charts, diagrams, and mind maps). Hearing or listening to information may be the best way of learning for auditory (A) learners. Such learners acquire much in lectures, prefer group discussions or listening to audio tapes and enjoy talking about examples. Besides, the read/write (R) learners grab information best when presented with words. They are often more successful in classes offering well-prepared slides or an appropriate writing outline. Finally, a kinesthetic (K) learner learns best by practice or simulation.[10, 13]

Students may also adopt different learning styles in unimodal or multimodal patterns.[14] While a multimodal learning style was previously reported to be more prevalent in studies involving medical and dentistry students,[15-17] some other studies mentioned the common adoption of a unimodal learning style.[14, 18] Students with a multimodal learning style have the ability to process information in any learning style and can adjust themselves to diverse teaching styles for a certain period of time.[14] In this study, it was discovered that the multimodal learning style was adopted more than the unimodal learning style (70.30% vs. 29.70%), implying that electrophysiology students may enjoy a curriculum including theoretical and practical courses enriched with teaching with the mentioned perceptual styles.

As mentioned, learning styles can be considered key to deciding upon distance learning environments. Thus, further studies may consider scrutinizing learning preferences and learning styles in online learning environments using instruments to measure online learning styles.[2]

Attitudes toward online learning are thought to be influential in distance learning, as well as learning styles.[5] It was found that the participants had the highest and lowest scores on the APPEFF and INDAWR subscales, respectively. Besides, the participants had high attitudes toward online learning. While various studies indicated moderate attitudes toward online learning among nursing students, some studies concluded that the participants exhibited 'indecisive' or negative attitudes.[19-22] Mubayrik et al. reported that 67.9% of the participating medical students attended distance education and exhibited positive attitudes toward the "efficiency" of distance education. The top themes from the participants' views on distance education were 'accessibility,' 'ability to attend classes from anywhere,' and 'the ability to teach from anywhere.' Most respondents also appreciated the convenience of online learning regarding flexibility. In addition, the author reported a significant positive association between attending online classes and attitudes toward distance education.[23] In this study, the majority of the participants had attended distance education programs before; that is, they had experienced online classes. The hypothesis that students with the opportunity to experience online classes may adopt more positive attitudes toward online learning was confirmed in other studies as well as in this study.[22] In other words, a previous experience with online learning may have contributed to their positive attitudes toward online learning.

Considering the students' attitudes toward online learning by gender, while they did not significantly differ in total OLAS scores, the male students had significantly higher scores on the USEFUL subscale than the female students. In their study investigating nursing students' attitudes toward online learning, Kabasakal et al. found no significant difference in total OLAS scores by gender, similar to this study.[20] The higher scores of the male students on the USEFUL subscale in this study may be attributed to an advantage of distance education: independent learning.[24] In the same study,[20] the authors concluded different mean attitude scores between the juniors and seniors. In this study, however, there was no significant difference in the attitude scores of the first-year and second-year students, which may be because the participants were at almost similar years of their study.

In their study exploring the effects of learning styles on the attitudes toward e-learning, Brown et al.[25] concluded that health science students' learning styles (measured with the Index of Learning Styles) could be considered to a limited extent as a predictor of their attitudes toward e-learning (measured with the Online Learning Environment Survey). In that study, the authors highlighted that the lecturers of health science students may consider the students' learning styles, particularly when utilizing technology or other aspects of e-learning. In another study using Kolb's Learning Style Inventory, students adopting 'assimilative' and 'accommodative' learning styles demonstrated significantly more welcoming attitudes toward various aspects of network-based teaching than those adopting 'convergent' and 'divergent' learning styles.[26] In their study with medical students, Yurdal et al. showed that learning styles were significant predictors of attitudes toward online education and determined that the visual-auditory learning style had the highest predictive power for

such attitudes.[27] The findings in this study showed that the participants adopting bimodal and quadrimodal styles had higher attitudes toward online learning than their counterparts with a unimodal style, implying that planning and executing learning processes covering all four learning styles may bring substantial advantages for teaching electrophysiology.

In summary, the findings revealed that the participating electrophysiology students mostly adopted a multimodal learning style, that they showed higher attitudes toward online learning, which did not significantly differ by year of study and gender, and that the students adopting a multimodal style had higher attitudes toward online learning than the unimodal learners.

The only limitation of the present research may be the relatively low sample size due to the single-center design.

Overall, the participating electrophysiology students' high attitudes toward online learning may document that online learning can be utilized as an efficient method in electrophysiology education. In addition, designing online teaching processes based on electrophysiology students' favorable learning styles may contribute to their productivity.

Ethical Considerations: The Ethics Committee of Health Sciences University granted ethical approval to this study (2022-113 dated 04.21.2022).

Conflict of Interest: None declared.

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Research Article

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THE IMPACT OF CONTACT LENS DURATION ON OCULAR DISCOMFORT

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Abstract

Objectives: To compare contact lens discomfort (CLD) using the Contact Lens Dry Eye Questionnaire-8 (CLDEQ8) in short and long-term CL wearers.

Materials and Methods: This prospective study included 98 patients who applied to the Department of Ophthalmology of Ufuk University between January 2020 and January 2021 and had a history of wearing contact lenses for over a month. Participants who wore contact lenses (CL) for six months or less were categorized as short-term CL users, while those who wore them for more than six months were categorized as long-term CL users. Contact lens compliance and the CLDEQ-8 questionnaire results were compared between the groups.

Results: The mean age was 21.70±2.81 years in 55 short-term CL wearers, and 80% were female. In 43 long-term CL wearers, the mean age was 28.69±8.48 years, and 86% were female (respectively, $p<0.001$, $p=0.592$). The duration of CL wear was 2.36±1.06 months in short-term CL wearers and 10.11±5.6 months in long-term CL wearers ($p<0.001$). The mean CLDEQ-8 score was 11.52±6.59 in short-term CL wearers and 14.37±6.55 in long-term CL wearers ($p=0.015$). In addition, 40% of short-term and 65.1% of long-term users had a CLDEQ-8 score greater than 12 ($p=0.016$).

Conclusion: Long-term CL wearers experienced much more CLD, and several considered removing their lenses at various times. Contact lens discomfort has to be investigated, especially in long-term CL users, and solutions should be developed to avoid CL dropout.

Keywords: Contact lens, long-term contact lens users, contact lens discomfort, CLDEQ-8.

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Introduction

Contact lenses (CL) have several benefits over glasses, such as more excellent peripheral vision, use while playing sports, allowing the wearing of sunglasses, and improved quality of life status compared to glasses.[1] Because of these advantages, soft CL is among the most widely used means of correcting refractive problems, and evolving lens technology raises CL users' expectations and prevalence.[2]

Ocular surface discomfort and dry eye have increased in frequency due to lifestyle changes, increased use of digital screens, climate changes, and the impact of the coronavirus pandemic and have more negative effects on life quality.[3-6] The prevalence of discomfort and dryness among soft CL wearers is higher than those of similar age who were not using CL.[7] Contact lens discomfort (CLD) is a term that encompasses several adverse ocular sensations, such as perception, awareness, and sensation of the CL on the ocular surface.[8] Contact lens wearing time can be restricted due to CLD, which may influence the success of treatment and even lead to discontinuation of CL wear.[9]

The Contact Lens Dry Eye Questionnaire (CLDEQ) was developed to measure dryness symptoms among contact lens wearers, and CLDEQ-8 is a short version of the CLDEQ questionnaire, which allows a quick standardized means to measure symptom-based condition from the wearer's point of view and to screen CL-related dry eye.[10, 11]

The study aimed to compare CLD using the CLDEQ-8 questionnaire in short- and long-term CL wearers.

Materials and Methods

This prospective study was conducted in the Department of Ophthalmology of Ufuk University between January 2020 and January 2021. Approval was obtained from the local ethics committee, and all of the study procedures were conducted in accordance with the Declaration of Helsinki.

All CL wearers who used CL regularly for more than one month were included in the study. The patients with ocular surface diseases, including dry eye, orbitopathy or eyelid diseases, and those using medications that can cause dry eye or those using eye drops with preservatives were excluded.

All participants underwent ophthalmological examination. Their contact lens use habits were questioned, and they were asked to fill out the Turkish version of the CLDEQ-8 questionnaire. Participants who wore CL for six months or less were categorized as short-term CL users, while those who wore them for more than six months were categorized as long-term CL users. The cut-off value for the CLDEQ-8 sum score was accepted as 12.[12]

Descriptive and statistical analysis was performed using IBM SPSS Statistics 21. Normality was tested with the Shapiro-Wilk test. Age, duration of CL wear, and CL wearing time were presented as mean and standard deviation. Independent variables were evaluated with Mann-Whitney U and categorical variables with the Chi-square test. Statistical significance was accepted as a p-value of 0.05 or less.

Results

Ninety-eight CL wearers have been included in the questionnaire. The mean age of the participants was 24.77±6.90 years, and 82.6 % were female. Most participants hold an undergraduate university degree (28.5%) or are pursuing an undergraduate degree (62.2%). Of 84.7% of patients who wore spherical CL, 8.2% toric CLs, 4.1% multifocal spherical CL, 1% multifocal toric CL and 2% did not answer the question.

The mean age was 21.70±2.81 years in 55 short-term CL wearers, and 80% were female. In 43 long-term CL wearers, the mean age was 28.69±8.48 years, and 86% were female (respectively, $p<0.001$, $p=0.592$). The duration of CL wear was 2.36±1.06 months in short-term CL wearers and 10.11±5.6 months in long-term CL wearers ($p<0.001$). Contact lens wearing time was 11.52±5.10 hours per day and 6.16±1.15 days per week in short-term CL wearers, 11.76±3.07 hours per day and 6.25±1.32 days per week in the other group (respectively, $p=0.185$, $p=0.357$).

None of the participants reported that they wore their CL overnight. Among short-term CL wearers, 81.8% change solutions in the CL case daily or every other day, and 81.8% rinse the CL case at least once a week. 86% of long-term CL wearers change solutions in CL cases daily or every other day, and 79% rinse CL cases at least once a week. The two groups had no statistically significant difference regarding these behaviors (respectively $p=0.784$, $p=0.80$). All participants used a multipurpose solution to rinse their CL case and CL. The optician was the primary source of CL for the participants in both groups (89% of short-term, 73.8% of long-term CL wearers, $p=0.176$).

The mean CLDEQ-8 score was 11.52±6.59 in short-term CL wearers and 14.37±6.55 in long-term CL wearers ($p=0.015$). In addition, 40% of short-term and 65.1% of long-term users had a CLDEQ-8 score greater than 12 ($p=0.016$). When the responses to the questionnaire's questions were analyzed, there was an essential difference in response to question 5. While 60% of short-term CL users never thought they should take out their contact lenses when doing something, this rate was 10% for long-term CL users. The CLDEQ-8 questionnaire is given in Table 1.

Table 1. Contact lens questionnaire-8 (CLDEQ-8)

Questions		Response
1-Questions about EYE DİSCOMFORT	a. During a typical day in the past 2 weeks, how often did your eyes feel discomfort while wearing your contact lenses?	0 Never 1 Rarely 2 Sometimes 3 Frequently 4 Constantly
	b. When your eyes felt discomfort with your contact lenses, how intense was this feeling of discomfort at the end of your wearing time?	0 Never have it 1 Not at all intense 2 3 4 5 Very intense
2-Questions about EYE DRYNESS	a. During a typical day in the past 2 weeks, how often did your eyes feel dry?	0 Never 1 Rarely 2 Sometimes 3 Frequently 4 Constantly
	b. When your eyes felt dry, how intense was this feeling of dryness at the end of your wearing time?	0 Never have it 1 Not at all intense 2 3 4 5 Very intense
3-Questions about CHANGEABLE, BLURRY VISION	a. During a typical day in the past 2 weeks, how often did your vision change between clear and blurry or foggy while wearing your contact lenses?	0 Never 1 Rarely 2 Sometimes 3 Frequently 4 Constantly
	b. When your vision was blurry, how noticeable was the changeable, blurry, or foggy vision at the end of your wearing time?	0 Never have it 1 Not at all intense 2 3 4 5 Very intense
4-Question about CLOSING YOUR EYES	During a typical day in the past 2 weeks, how often did your eyes bother you so much that you wanted to close them?	0 Never 1 Rarely 2 Sometimes 3 Frequently 4 Constantly
5-Question about REMOVING YOUR LENSES	How often during the past 2 weeks, did your eyes bother you so much while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and take out your contact lenses?	1 Never 2 Less than once a week 3 Weekly 4 Several times a week 5 Daily 6 Several times a day

Discussion

CLD is episodic or persistent adverse ocular sensations related to contact lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear.[13]Risk factors for CLD can be categorized as contact lens-related, patient-related or associated with contact lens hygiene or replacement, and patient-related factors are the most difficult to assess and improve.[14] In the present study, long-term CL wearers experienced much more CLD, and several considered removing their lenses at various times. In contrast, a meta-analysis showed that increasing age was associated with increased lens fit in experienced contact lens wearers.[15] Considering long-term users, lens dropout, which might be a bias factor, might be the source of the difference between these two outcomes. The mean lens wear time of long-term users in the study was 10 months and which was less than two years, which is the mean dropout time for long-term users.[13]

CLD is one of the causes of contact lens dropout.[16] A study investigating the reasons for lens dropout in neophytes reported that half of those who left CL was discontinued within the first two months, and 21% of the causes of lens dropout were reported as CLD.[17] Among the causes of lens dropout in long-term contact lens wearers, CLD is more prominent.[13] In line with the literature, while 60% of short-term users never considered removing their CL due to CLD, most long-term users stated that they thought about occasionally removing their CL with varying frequency in the present study. However, since participants who dropped out of CL were not included in the study, such a difference may have been detected, as people who used contact lenses for a short period and then dropped out might have been ignored.

Contact lens wear can impact the morphology and functioning of the meibomian glands. A decrease in functional meibomian glands is proportional to the duration of CL wear.[18,19] Changes in meibomian gland function might impact tear film and cause symptoms of ocular discomfort. The CLDEQ-8 is an essential tool for evaluating patients who are symptomatic but have no clinical findings. A study showed that patients with a high CLDEQ-8 score but without clinical signs have a loss of meibomian glands in the lower lid.[20] In our study, although there were no clinical findings in the patients, the CLDEQ-8 score was significantly higher in long-term CL users. These results may be due to a subclinical meibomian gland dysfunction. Although the alterations in the morphology and function of the meibomian gland with advanced age are also known[21], despite the significant age difference in our study, the effect of age can be ignored because the mean age of long-term users is young (mean age=28). The increase in the CLDEQ-8 score may alter meibomian gland function due to the long duration of CL wear.

Prolonged contact lens wearing time has been reported as one of the causes of CLD.[22] In this context, the present study found no significant difference between the two groups. No significant relationship has been reported

between compliance factors and CLD.[22] In line with the literature, both groups had similar CL compliance in the current study.

One of the study's limitations is that the two groups are different in age. However, this situation may be insignificant since the two groups were in the same decade. Another limitation of the study was the relatively short mean lens wear time of long-term users (mean ten months). The study's strength is that most patients had similar educational statuses and created a homogeneity in daily activities that may affect CLD, such as digital screen usage and reading habits.

Contact lens discomfort is more common in long-term contact lens wearers. In long-term CL users, CLD needs to be questioned, and remedies should be sought to prevent CL dropout.

Ethical Considerations: Ethical approval for this study was obtained from Ufuk University's non-interventional ethics committee (App. No: 02022017-4).

Conflict of Interest: The authors declare no conflict of interest.

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Research Article

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THE EFFECT OF POSTNATAL EDUCATION ON BREASTFEEDING SELF-EFFICACY AND PREDICTORS OF NEWBORN WEIGHT CHANGES IN THE FIRST 10 DAYS: A PROSPECTIVE STUDY

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Abstract

Objectives: To investigate the role of postnatal verbal and visual education in improving breastfeeding self-efficacy (BSE) and factors effective in weight gain or loss in the first ten days.

Materials and Methods: Conducted between March-June 2020, this prospective study included a total of 145 healthy women with third-trimester pregnancies who received postpartum breastfeeding education (verbal and visual). Prenatal (pre-training) and postnatal (post-training) BSE Scale-Short Form (BSES-SF) scores, birth weights, The Edinburgh Postnatal Depression Scale and LATCH scale scores at the 10th day after birth, 10th-day newborn weight and differences in birth weight were recorded. Grouping was done according to whether or not the newborn reached birth weight at day 10 (decreased weight: DW group, same or increased weight: SIW group).

Results: Mean maternal age was similar in the DW (30.61 ± 4.72) and the SIW groups (30.47 ± 4.88). Median BSES-SF scores after training were significantly higher than before training ($p<0.001$). Multiple logistic regression analysis revealed that regular follow-up during pregnancy ($p=0.014$) and high LATCH score ($p<0.001$) were independently associated with being in the SIW group on the 10th day, whereas additional formula feeding ($p=0.006$) and high EPDS score ($p=0.004$) were independently associated being in the DW group.

Conclusion: BSE can be improved by using postnatal verbal and supervised video breastfeeding training. LATCH and EPDS scores can be used to easily identify mothers at high risk for postpartum breastfeeding problems and depression.

Keywords: Postnatal education, breastfeeding self-efficacy, infant weight change, Edinburgh Postnatal Depression Scale, LATCH scale.

Introduction

Breastfeeding supports neurological, psychomotor, social, intellectual and immunological development, reduces the incidence of neonatal complications, child mortality and morbidity, and the risk of developing many chronic diseases in later stages of life and also provides many maternal benefits.[1-3] Therefore, promoting breastfeeding and its duration and quality should be one of the most basic objectives of the relevant healthcare providers.

Various social, physical, biological and psychological factors affect breastfeeding initiation and maintenance.[3,4] Breastfeeding self-efficacy (BSE) is an important psychological factor with a strong predictive effect in this regard.[4] It reflects the mother's self-confidence about breastfeeding.[2,5] Low BSE is associated with initiating and/or continuing breastfeeding.[1,5,6] However, BSE can be improved with antenatal and postnatal interventions.[4,6,7] Two systematic reviews showed the most effective intervention is face-to-face and supervised visual breastfeeding training (BFT).[2,4]

Newborn weight gain (WG) in the first ten days is a critical factor that is closely monitored in routine follow-ups, and it is well-established that breastfeeding contributes to healthy WG. LATCH score is a breastfeeding assessment tool that has been used to assess breastfeeding practices.[8] Studies have explored various factors that are associated with WG, including LATCH score, postpartum maternal depression (PMD), duration of exclusive breastfeeding, formula versus breastfeeding, and prematurity.[8-10] Weight loss (WL) or insufficient WG in the first weeks adversely affects neurologic and cognitive development, which may also be associated with early termination of breastfeeding.[11] Thus, it is of particular importance to identify factors associated with WG and to include these in the assessment of newborn development, thereby enabling better management. However, most studies in the literature have specifically assessed a few of these possible factors and/or have evaluated weight changes in later periods.[8-10]

In this study, with the intention of contributing to breastfeeding rates in our hospital, our country and worldwide, we aimed to investigate the role of postnatal face-to-face verbal and visual education in improving BSE and to investigate whether other factors were also effective in WG or WL in the first 10 days.

Materials and Methods

Study design

This prospective observational study was conducted at a neonatology clinic during the period from March 2020 to June 2020 after taking written informed consent from all included participants. Ethical approval for this study was provided by the Research Ethics Committee of Yıldırım Beyazıt University.

Study population

A total of 145 healthy women in the third trimester of pregnancy, all of whom attended pregnancy follow-up and were scheduled for delivery at the Obstetrics and Gynecology Department of our hospital, were included in the study, given that they volunteered to participate. Since the reproductive period is considered to be between the ages of 18 and 45, women under the age of 18 and over the age of 45 were not included in our study. The exclusion criteria were as follows: Being <18 or >45 years old, having major obstetrical or medical pregnancy complications, having mental retardation or any psychiatric illness, being scheduled for or undergoing non-full-term births (gestational age <37 or ≥42 weeks) due to various reasons, delivery with abnormal birth weight (<2500 gr or >4000 gr), giving birth to a newborn with complications and/or congenital abnormality (determined by medical and clinical examinations), complicated delivery process, and lack of information regarding relevant data or in case of discrepancy.[12,13] Since each pregnancy was considered as a separate period, previous pregnancy status was not considered as an exclusion criterion.

Study procedure and data collection instruments

The study procedure consisted of 3 phases. In the first phase, related to the prenatal period, women were asked to fill out a personal information form including demographic data, socioeconomic and educational status, previous pregnancy and birth information and data about the current pregnancy. Also, all women completed the BSE Scale-Short Form (BSES-SF) at any time within the last trimester. In the second phase, conducted after delivery and before discharge, birth information and newborn weight were recorded, and the women were given BFT by nurses who are trained and certified by the ministry of health verbally and additionally by having them watch a training video about breastfeeding prepared in line with the World Health Organization (WHO) recommendation. Under the responsibility of obstetricians and obstetricians who have completed the birth preparation certificate program organized by the ministry, opened within the body of public hospitals providing pregnant school, gynecology and obstetrics services, universities and private hospitals, and in the presence of a responsible midwife, prenatal, birth preparation, delivery and delivery to the pregnant/pregnant candidate/relatives These are the units that provide training and consultancy services for the post-secondary period.[14] Then, they were asked to fill out the BSES-SF again. The discharge was scheduled as follows: if there was no contraindication, those with normal vaginal delivery were discharged 24 hours after delivery, and those with cesarean section delivery were discharged 48 hours after delivery. As a rule of thumb, newborns usually lose 10.00% of their birth weight in the first week after birth and are expected to reach their birth weight by

10 to 14 days after birth under normal conditions.[15] At the third phase (i.e., on the 10th-day follow-up after birth), the newborn weight was measured, and the feeding features data were recorded. The mothers were asked to complete the LATCH Breastfeeding Diagnostic Tool and The Edinburgh Postnatal Depression Scale (EPDS).

The mothers were divided into two groups, "the decreased weight (DW)" group and "the same or increased weight (SIW)" group, as a result of the comparison of their weight measured on the 10th day and their birth weight. Healthy babies were called for control on the 10th day by the hospital for routine control.

The Breastfeeding Self-Efficacy Scale-Short Form

The BSES-SF is a reliable measure to assess BSE. The scale is a self-reported tool and consists of 14 items, each of which grades the mother's self-confidence level on a subject from 1 to 5. The lowest score of 14 indicates that the mother is not at all confident about breastfeeding, while the highest score of 70 indicates that she is perfectly confident about breastfeeding.[5]

The Edinburgh Postnatal Depression Scale

The EPDS, a self-reported depression scale, is used for identifying postpartum maternal depression (PMD). The Edinburgh Postnatal Depression Scale was first developed (1987) by Scottish health centers in Edinburgh and Livingston, and it is still up to date. It consists of 10 questions, and each scored between 0-3. Higher scores represent an increased risk of PMD. In this study, we used the cut-off value of ≥13 as the value that corresponds to a high risk for major postpartum depression.[16,17]

LATCH Breastfeeding Diagnostic Tool

It was developed by Jensen and Wallace (1994), and it is still up to date. The LATCH is a charting system developed to gather information about individual breastfeeding sessions, in which five criteria are evaluated (L: Latch on breast, A: Audible swallowing, T: Type of nipple, C: Comfort breast/nipple, H: Hold/help). Each criterion is scored as 0, 1, or 2 points. Zero points indicate the worst quality of breastfeeding, and 10 points the best.[18]

Outcomes

The primary aim of the study was to investigate the effect of postnatal breastfeeding education on BSE. The secondary aim was to investigate the most powerful predictors of weight change in the first 10-day period.

Statistical Analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA), and significance was set at $p < 0.05$. The normality of distribution for continuous data was determined with the Shapiro-Wilk test. According to the results, mean ± standard deviation (normal distribution) or median and first quartile – third quartile values (non-normal distribution) were used to summarize data. Frequency (percentage) was used for categorical variables. Repeated measurements were analyzed with the paired samples t-test (normal distribution), or the Wilcoxon signed ranks test (non-normal distribution). Between groups, analysis of continuous variables was performed with the independent samples t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution). Between groups, analysis of categorical variables was performed with chi-square tests or Fisher's exact test. Multiple logistic regression analysis (forward conditional) was performed to determine factors independently associated with the weight change on the 10th day.

Results

The mean age of the mothers was 30.51 ± 4.82 years. The mean weights of newborns at day 10 were significantly higher than the mean birth weights ($p<0.001$). The BSES-SF score of 141 (97.24%) women increased, 3 (2.06%) remained the same, and 1 (0.69%) decreased following training. Median post-training BSES-SF scores were significantly higher than pre-training scores ($p<0.001$) (Table 1, Table 2).

Table 1. Descriptive Data

Age (mean±SD)	30.51 ± 4.82
Education status [**n** (%)]	
Primary school	19 (13.10%)
Secondary school	36 (24.83%)
High school	58 (40.00%)
University	32 (22.07%)
Occupation [**n** (%)]	
Public service (government employee)	21 (14.48%)
Worker (labor)	10 (6.90%)
Housewife	114 (78.62%)
Economic status [**n** (%)]	
Poor	3 (2.07%)
Moderate	101 (69.66%)
Good	41 (28.28%)
Health insurance	145 (100.00%)
Adult (other than husband) living at home	11 (7.59%)

(Data are given as mean ± standard deviation and as frequency (percentage) for categorical variables.)

Table 2. Obstetric History Data

Number of children	
1	20 (13.79%)
2	95 (65.52%)
3	23 (15.86%)
4	7 (4.83%)
Abortion/Curettage	48 (33.10%)
Exclusive breastfeeding for six months [1]	84 (67.20%)
Duration of breastfeeding, months [1,2]	14 (9 - 20)
Regular follow-up during pregnancy	138 (95.17%)
Attending a "pregnancy school"	24 (16.55%)
Type of birth	
Vaginal	60 (41.38%)
Cesarean section	85 (58.62%)
Planned pregnancy	108 (74.48%)
Gestational week at birth	39 (38 - 40)
Stay in the neonatal intensive care unit	22 (15.17%)
Whom do you ask for advice in the presence of breastfeeding problems? [3]	
Family/Friends	42 (28.97%)
Family health center nurse	75 (51.72%)
Family physician	11 (7.59%)
Obstetrician and gynecologist	4 (2.76%)
Pediatrician	23 (15.86%)
Breastfeeding polyclinic	50 (34.48%)
Paid breastfeeding consultant	0 (0.00%)
Who do you apply to for nipple problems? [3]	
Family/Friends	48 (33.10%)
Family health center nurse	18 (12.41%)
Family physician	57 (39.31%)
Obstetrician and gynecologist	22 (15.17%)
Pediatrician	18 (12.41%)
Breastfeeding polyclinic	7 (4.83%)
Paid breastfeeding consultant	0 (0.00%)
Weight, g	
At birth	3347.54 ± 390.67
10th day	3460.14 ± 412.54
Change in weight	
Decreased	41 (28.28%)
Same	2 (1.38%)
Increased	102 (70.34%)
Feeding other than breast milk	
Water	0 (0.00%)
Formula	36 (24.83%)
Other	0 (0.00%)
Who advised other feedings? [4]	
Family	7 (19.44%)
Friend	1 (2.78%)
Physician	28 (77.78%)
The Breastfeeding Self-Efficacy Scale score	
Before training	56 (49 - 60)
After training	62 (58 - 65)
The Edinburgh Postnatal Depression Scale score	2 (0 - 7)
Postpartum depression (≥13 points)	12 (8.28%)
LATCH score	10 (9 - 10)

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

[1] Data are collected for children from earlier pregnancies. 20 mothers who had first child are not included into the assessment.

[2] Median values are used for multiple children.

[3] Participants are allowed to choose multiple options.

[4] Only 36 mothers who gave formula to their child included into the assessment.

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Table 3. Summary of variables and analysis results with regard to weight gain categories on the 10th day

	Change in weight		
	Decreased (n=41)	Same & Increased (n=104)	p
Age	30.61 ± 4.72	30.47 ± 4.88	0.877
Education status			
Primary school	4 (9.76%)	15 (14.42%)	**0.028**
Secondary school	16 (39.02%)	20 (19.23%)	
High school	17 (41.46%)	41 (39.42%)	
University	4 (9.76%)	28 (26.92%)	
Occupation			
Public service (government employee)	6 (14.63%)	15 (14.42%)	0.280
Worker (labor)	5 (12.20%)	5 (4.81%)	
Housewife	30 (73.17%)	84 (80.77%)	
Number of children			
1	10 (24.39%)	10 (9.62%)	**0.040**
2	20 (48.78%)	75 (72.12%)	
3	8 (19.51%)	15 (14.42%)	
4	3 (7.32%)	4 (3.85%)	
Abortion/Curettage	15 (36.59%)	33 (31.73%)	0.716
Economic status			
Poor	1 (2.44%)	2 (1.92%)	**0.026**
Moderate	35 (85.37%)	66 (63.46%)	
Good	5 (12.20%)	36 (34.62%)	
Adult (other than husband) living at home	6 (14.63%)	5 (4.81%)	0.075
Regular follow-up during pregnancy	36 (87.80%)	102 (98.08%)	**0.020**
Attending a "pregnancy school"	2 (4.88%)	22 (21.15%)	**0.033**
Type of birth			
Vaginal	12 (29.27%)	48 (46.15%)	0.095
Cesarean	29 (70.73%)	56 (53.85%)	
Planned pregnancy	29 (70.73%)	79 (75.96%)	0.661
Gestational week at birth	39 (38 - 39)	39 (38 - 40)	0.633
Stay in the neonatal intensive care unit	11 (26.83%)	11 (10.58%)	**0.028**
Addition of formula feeding	22 (53.66%)	14 (13.46%)	**<0.001**
The Breastfeeding Self-Efficacy Scale score			
Before training	53 (48 - 58)	57 (51 - 60)	**0.013**
After training	58 (54 - 62)	63 (60 - 65)	**<0.001**
The Edinburgh Postnatal Depression Scale score	8 (2 - 12)	0.5 (0 - 4.5)	**<0.001**
Postpartum depression (≥13)	7 (17.07%)	5 (4.81%)	**0.038**
LATCH score	9 (7 - 10)	10 (10 - 10)	**<0.001**

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

There was no significant difference between the mean age of the DW group (30.61 ± 4.72) and the SIW group (30.47 ± 4.88) (p = 0.877). The percentage of women with university degrees (p = 0.028), who had two children (p = 0.040), had a good economic status (p = 0.026), attended regular obstetric follow-up (p = 0.020), and attended a "pregnancy school" (p = 0.033) was significantly higher in the SIW group. A pregnancy school is a place planned by the Ministry of Health and organized by provincial health directorates, where pregnant women are informed collectively and as standard by certified nurses/doctors. The percentage of women with

secondary school degrees (p = 0.028), whose babies were admitted to the neonatal intensive care unit (NICU) (p = 0.028) and who fed formula (in addition to breastfeeding) (p < 0.001) were higher significantly in the DW group. Both pre-training (p = 0.013) and post-training (p < 0.001) BSES-SF scores and LATCH scores (p < 0.001) of the SIW group were significantly higher than the DW group. Both the median EPDS score (p < 0.001) and the percentage of women who were diagnosed with PMD (p = 0.038) were significantly higher in the DW group (Table 3).

Multiple logistic regression analysis revealed that regular follow-up during pregnancy (p = 0.014) and high LATCH score (p < 0.001) were independently associated with being in the SIW group, while additional formula feeding (p = 0.006) and high EPDS score (p = 0.004) were independently associated with being in the DW group (Table 4). Other variables included in the analysis, such as education (p = 0.144), number of children (p=0.665), economic status (p = 0.109), attending pregnancy school (p = 0.134), stay in NICU (p = 0.685), BSES-SF scores before training (p = 0.691) and after training (p = 0.252) and PMD (p = 0.135), which were found to be non-significant.

Table 4. Significant factors independently associated with the weight gain category on the 10th day, multiple logistic regression

	β coefficient	Standard error	p	OR	95% CI for OR	
Regular follow-up during pregnancy	2.687	1.091	**0.014**	14.694	1.732	124.679
Addition of formula feeding	-1.519	0.555	**0.006**	0.219	0.074	0.649
Edinburgh Postnatal Depression Scale score	-0.159	0.055	**0.004**	0.853	0.766	0.950
LATCH score	1.188	0.282	**<0.001**	3.281	1.889	5.698

(CI: Confidence Interval, OR: Odds Ratio, Dependent variable: Same & Increased weight on 10th day, Nagelkerke R^2=0.558)

Discussion

Breastfeeding success and WG in the first weeks of life are two factors having a reciprocal relationship, and abnormalities in these may have negative effects during infancy and later life.[1,2,11] Therefore, we aimed to show the effect of breastfeeding education on BSE and the most important factors associated with newborn weight changes in the first ten days. As a result, postpartum BFT significantly improved BSES-SF scores. Regular follow-up during pregnancy and high LATCH score were the most important predictors of WG (or weight stability); whereas formula feeding and high EPDS score were the most important predictors of WL in the first ten days.

Knowledge, self-efficacy and intention on breastfeeding, maternal age, occupation and parity have been identified as factors significantly related to breastfeeding duration and exclusivity.[3] The theory of BSE hypothesizes that BSE findings are associated with the mother's thoughts about breastfeeding and her effort to breastfeed and that these effects influence the initiation and maintenance of breastfeeding.[19] This theory has been supported by various studies.[7,20] In the literature, viewing images portraying breastfeeding, receiving professional help, the mother's age and occupation, social support, skin-to-skin contact with the baby and previous breastfeeding experience have been presented as factors affecting BSE.[3,21] In this study, we showed postpartum verbal breastfeeding education and supervised visual video training caused significant positive changes in BSES-SF scores. Although many studies have shown that BFT improves BSE, two reviews showed that face-to-face training was more effective in improving BSES scores than other types of interventions.[2,4,6,7,20] Our results support these reviews' results. Implementation of antenatal and/or postnatal face-to-face and/or video-assisted BFT to improve BSE may increase breastfeeding prevalence and duration.

Improving BSE may increase breastfeeding success. In this study, we did not conduct research on breastfeeding outcomes; therefore, we could not demonstrate the effect of improvement in the BSES-SF score on breastfeeding outcomes. However, pre- and post-training BSES-SF scores were not identified as predictors of weight status. In a review aiming to reveal the theoretical link between BSE and breastfeeding rates, it was concluded that BSE-improving interventions, especially those focused on education, increase breastfeeding rates at 1 and 2 months postpartum.[2] Pregnant women with low confidence in their ability to breastfeed are more likely to stop breastfeeding before two weeks postpartum, and women with high BSE are more successful at initiating and maintaining breastfeeding.[22] However, the relationship between the BSES score and weight changes in the early stages of life is unclear. Clarifying the relationship between BSE and weight changes may contribute to the creation of new systems demonstrating the relationship between BSE, breastfeeding success and weight changes in the first weeks of life more successfully.

The most basic goal of infant feeding is sufficient WG within the specified time periods. Adequate WG is directly related to the adequate amount of breast milk and delivery of this milk to the child.[23] The LATCH scale determines a breastfeeding quality score that is a combination of the child's and mother's abilities.[18] There is a significant relationship between average LATCH scores and the time of breastfeeding initiation.[23] We determined the 10th-day LATCH score as an independent factor for WG in the first ten days. Similar to this result, in a prospective study, a high LATCH score at discharge was significantly positively associated with both exclusive breastfeeding rate and WG velocity at six weeks of age, although our weight assessment was in a different period.[8] Moreover, the median LATCH score was 10 in the current study, which is higher than previously reported.[23] This may be a result of BFT, but further studies with control groups are needed to draw definitive conclusions. Breastfeeding discontinuation rates are highest in the first month after birth.[8] Thus, it is critical to identify breastfeeding problems and mothers who will need professional support in the early

postpartum period.[8] The literature shows that the LATCH scale, an easily applicable and reliable system, can help prevent early cessation of breastfeeding by detecting mothers having breastfeeding problems and also taking precautions for the risk of WL.[23]

In the present study, 8.28% of mothers were at high risk for major postpartum depression. Also, the EPDS score was an independent risk factor associated with lower WG in the first ten days of life. Wright et al. reported that the mothers of infants with slower WG and increased rates of weight faltering up to 4 months had higher EPDS scores.[9] In yet another study, the depressed mood of the mothers was found to be associated with reduced infant WG.[11] The negative effect of depression on infant WG has been explained by several pathophysiological mechanisms.[9,11,21] It is even possible that in this mechanism, depression is a result rather than a cause.[9,11] Moreover, PMD can reduce BSE.[21,24] We also want to emphasize that the rate of PMD in some other studies is higher than in the current study. There are several possible reasons for this.[9,24] The first may be that the EPDS in this study was applied at an earlier period. Secondly, the improvement in BSE provided by postnatal BFT and the highly likely positive effects of this improvement on breastfeeding may have positively affected EPDS scores. Finally, the variation in the frequency of PMD between countries and cultures may be another reason.[25] Due to these negative effects of PMD on breastfeeding success and WG, taking precautions for factors known to increase the risk of PMD and determining the risk of PMD and initiating the necessary treatments will be very beneficial for both the newborn and the mother.[24]

Many other factors also affect adequate milk intake and, so, adequate WG. Maternal socio-demographic features, time of breastfeeding initiation, baby's ability to suckle, breastfeeding technique and frequency, and breast and maternal-related factors are among these factors.[23,26] In this study, regular follow-up, LATCH score, formula use and EPDS score were the only factors independently associated with weight change. It would not be wrong to think that parents who have regular follow-ups are more conscious in terms of feeding and growth of their babies, and they could also be more likely to closely administer knowledge gained through training. Surprisingly, formula use was an independent predictor of reduced weight. It is expected that formula-fed infants gain more weight and be less likely to lose weight than solely breastfed infants.[10,27] However, an experimental study showed mothers feeding their babies only with breastmilk had higher postpartum BSES scores than those using formula. So, the indirect effects of formula over BSE may have adversely affected early WG. Also, the type of formula used and the amount of administration may be other factors to consider. Therefore, although our study shows that the addition of formula to breastfeeding is associated with being in the DW group, it is imperative that this result is interpreted with respect to the aforementioned factors that could influence the success of both formula feeding and breastfeeding, new and extensive studies are needed.

The possible limitations of the study were as follows. As a single-center study that included only healthy pregnant women and full-term and normal birth weight pregnancies, there is a considerable limitation

regarding the generalization of the results. Each pregnancy period of the individuals was evaluated separately, but the first pregnancy and subsequent pregnancies may differ in every aspect after the first pregnancy experience. The effect of postnatal education on only BSE was investigated. An untrained control group was not included. Of note, we also did not assess results with respect to absolute or relative WG but rather dichotomized patients as DW or SIW. Although this may be seen as a limitation, this dichotomization is based on well-established follow-up criteria for newborns. The effects of possible other factors on infant weight change were not investigated. Finally, the study presented results for only the first ten days of life, not longer-term results.[23,26,28-30]

In conclusion, significant improvement was observed in BSES-SF scores after training. Regular follow-up during pregnancy and high LATCH score were found to be independently associated with reaching sufficient WG, whereas high EPDS scores and formula use (in addition to breastfeeding) were found to be independently associated with insufficient WG during the examined period (birth to 10 days). BSE can be improved by using postnatal verbal and supervised video BFTs, thus contributing positively to breastfeeding outcomes. LATCH score and EPDS score can be used to easily identify mothers at high risk for postpartum breastfeeding problems and depression and can enable measures to prevent insufficient WG and other related risks. Further large-scale studies are needed for the classification of early WL, assessment of the effect of additional formula use, and utilization of regular follow-up during pregnancy.

Ethical Considerations: Ethical approval for this study was provided by the Research Ethics Committee of Yıldırım Beyazıt University (Date: 05/02/2020, approval No: 28).

Conflict of Interest: The authors declare no conflict of interest.

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COMPARISON OF RISK FACTORS FOR WARFARIN-ASSOCIATED BLEEDING

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Abstract

Objectives: Warfarin is the most commonly used oral agent for long-term anticoagulation. Nevertheless, bleeding is the most frequent side effect of warfarin, increasing mortality and morbidity and thereby restricting its use. Risk factors for bleeding include age, comorbid diseases, use of drugs that may interact with warfarin, and previous history of stroke or gastrointestinal bleeding. Using a questionnaire-based method, this study aimed to compare the risk of bleeding in two groups of warfarin users with and without a history of warfarin-related bleeding.

Materials and Methods: A total of 201 patients, including 100 who had bleeding during warfarin use in our outpatient clinic and 101 patients who were followed up with the international normalization rate, were included in the study. Risk factors in warfarin-related bleeding were evaluated by the researcher with a questionnaire created as a result of the literature review. Data were statistically analyzed.

Results: The prevalence of bleeding was 2.8 times higher in patients aged 65 years and older (confidence interval: 1.40-5.56) and 5.6 times higher in patients with comorbid diseases (confidence interval: 1.376-22.770). A history of stroke increased major bleeding 3.2 fold (confidence interval: 1.08-9.61). We also observed that lack of education might be a risk factor for warfarin-related bleeding.

Conclusion: We believe that older patients under warfarin treatment should be informed according to their education status, and their medications and comorbid diseases should be monitored regularly by the same centers.

Keywords: Warfarin, oral anticoagulation, bleeding, risk.

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Introduction

Thrombotic diseases are the leading cause of death today. In the United States (USA), six million people are affected by thrombotic events, and two million die annually.[1] It is clear how substantial the prevention and treatment of thrombotic events are. The use of rational methods of anticoagulant therapy is vital in life. Until recently, only one agent was used for long-term or life-long oral anticoagulation. In recent times, direct anticoagulant drugs have entered our lives.

Warfarin is used by millions of patients each year for chronic or paroxysmal atrial fibrillation, hypercoagulation conditions, prosthetic heart valves, recurrent deep vein thrombosis, and vascular diseases. Warfarin is a vitamin K antagonist required for synthesizing clotting factors II, VII, IX, and X, the endogenous anticoagulant proteins C and S.[2,3] The efficacy of warfarin, a drug with a narrow therapeutic range, is indicated by the international normalization ratio (INR). INR can be affected by drug interactions, diet, alcohol consumption, acute illnesses, liver disease, and changes in unknown factors. Therefore, warfarin dose adjustments should be made at regular intervals.[4] The most important complication of warfarin is bleeding. Bleeding rates during anticoagulation therapy range from 12 to 40%.[5,6] In five studies with warfarin atrial fibrillation (AF), the annual major bleeding rate was 1.3%, and the intracranial bleeding rate was 0.3%.[7] Monitoring regimens based on patient characteristics, intensity and duration of anticoagulant therapy, and simple prediction rules can reduce the risk of warfarin-induced bleeding.[8] Therefore, we wanted to investigate the risk factors that cause bleeding in cases of warfarin-induced bleeding in the region. The aim of this study, designed as a prospective study, was to investigate the factors that can trigger bleeding in warfarin use.

Materials and Methods

This study was carried out between November 2007 and September 2010 in a Research Hospital, Department of Internal Medicine, Division of Hematology, in Edirne, Turkey. A hundred patients admitted to Emergency Service with bleeding and hospitalized were included in the study. As the control group, 101 patients without bleeding who were followed in the outpatient clinics were taken.

Inclusion criteria for the study were; the use of warfarin, being 18 years of age or older, being a volunteer to participate in the study, and having a history of no other known hemostatic disorders leading to bleeding. While patients admitted to the hospital with warfarin-related bleeding were assigned to the patient group, patients without a history of warfarin-related bleeding were assigned to the control group.

An informed consent form was obtained from the patient and control groups. A questionnaire was prepared to determine the risk of warfarin users with and without bleeding. In this form, clinical and laboratory data were

determined in the case and control groups. Also, an in-group evaluation for specific data was carried out in the patient group. Study groups were examined according to the risk scoring system obtained from the study by Landefeld et al.[5]

Statistical Analysis

Statistical analyses were made using the statistical program STATISTICA AXA 7.1 with serial number AXA507C775506FAN3. Mann-Whitney U test was used to compare normal distributions of measurable data between groups, as the single sample Kolmogorov Smirnov test showed no normal distribution. Pearson $\chi 2$ and Fisher's exact $\chi 2$ tests were used for qualitative data. Spearman's Rho correlation analysis was used to evaluate the relationship between variables. Variables below $p<0.20$ were assessed by stepwise logistic regression to determine risk factors for warfarin-induced hemorrhage. Median (Min-Max) values and arithmetic mean ± Standard deviation was given as descriptive statistics. The significance limit for all statistics was selected as $p <0.05$.

Results

The study group consisted of 201 patients, 100 (49.75%) in the patient group and 101 (50.25%) in the control group. The mean age of the participants was 66.97±9.94 years in the patient group and 64.29±13.24 years in the control group. Half of the sample group were male participants. Most of the patients (n=121, 60.20%) were at 65 years or above 65 years. When the patient group was classified in terms of age, the difference found was statistically significant (p=0.001). When patients aged 65 years and over were compared with patients aged under 65 years, no significant difference was found between gender and bleeding (p=0.230), but the difference in educational level was statistically significant (p<0.001) (Table 1).

The INR value above 3.01 was higher in the patient group, whereas 3.0 and below was higher in the control group (Figure 1). When the distribution of INR levels was analyzed, it was found as 8.75±6.45 in the patient group and 2.25±1.77 in the control group (Figure 2). When the patient group was compared with the control group in terms of INR levels, the difference found was statistically significant (p<0.001) (Table 2).

When the INR follow-up rates of the patients were examined, it was observed that 64% of the patient group and 98% of the control group had INR follow-ups at a single center. Regarding the regularity of INR follow-up, 60% (n=60) of the patient group and 96% (n=97) of the control group had regular INR controls. The difference was statistically significant for follow-up at a single center (p=0.005) and regularity of follow-up (p<0.001) (Table 2).

Table 1. Demographic features

Characteristics		Patient Group n=100		Control Group n=101		Total		P*
Age (Years)		**Mean ± Sd**		**Mean ± Sd**		range		0.111
		66.97±9.94		64.29±13.24		18-69		
		n	**%**	**n**	**%**	**n**	**%**	p[a]
Age category	<65	33	33	47	46.53	80	39.80	**0.05**
	≥65	67	67	54	53.47	121	60.20	
Sex	Female	44	44	56	55.45	100	49.75	0.105
	Male	56	56	45	44.55	101	50.25	
Educational Status	Illiterate	21	21	11	10.89	32	15.92	0.027
	Literate	14	14	9	8.91	23	11.44	
	Primary or Secondary School	58	58	65	64.36	123	61.19	
	High School	3	3	13	12.87	16	7.96	
	High Education	4	4	3	2.97	7	3.48	

* Mann-Whitney U Test; [a]: Pearson Chi-Square Test; Sd: Standard deviation.

When the frequency of follow-up was analyzed, it was found that 40% (n=40) of the patient group and 77.2% (n=78) of the control group had a follow-up frequency of every 1-2 months. In terms of the frequency of INR follow-up, the difference was statistically significant (p<0.001) (Table 2).

The most common site of bleeding in the patient group was the upper gastrointestinal tract in 39% (n=39). The frequency of hematuria was 14% (n=14), and the rate of double or more focal bleeding was 22% (n=22). The difference in terms of the bleeding site was statistically significant (p<0.001) (Table 3).

Regarding the presence of a history of stroke, 23% of the objects in the patient group and 55.4% of the objects in the control group had a history of stroke. A statistically significant difference was found between the groups (p<0.001). When the patient group was compared in terms of stroke history, the difference was statistically significant (p<0.001) (Table 2).

As a result of binary comparisons, gender, age group (<65, ≥65), comorbid disease, and stroke were included in logistic regression analysis, and age and comorbid diseases were found to affect bleeding. Hemorrhage was 2.8 (confidence interval:1.409-5.563) times over 65 years of age and 5.597 (confidence interval:1.376-22.770) times more in patients with the comorbid disease.

In the paired comparisons, when the parameters which are less than p <0.20 were evaluated by logistic regression analysis, it was found that the history of stroke was increased by 3.224 (confidence interval: 1.081-9.61) fold in major bleeding (2 or more units require erythrocyte suspension).

Table 2. Possible risk factors for bleeding

Characteristics		Patient Group (n=100)		Control Group (n=101)		Total		p[a]
		n	**%**	**n**	**%**	**n**	**%**	
INR levels	<2.00	5	5	48	47.52	53	26.37	**<0.001**
	2.00-3.00	5	5	40	39.60	45	22.39	
	3.01-5.00	15	15	11	10.89	26	12.94	
	5.01-10.00	32	32	1	0.99	33	16.42	
	>10.00	43	43	1	0.99	44	21.89	
Follow-up status in a fixed center	Yes	64	39	99	98.02	163	81.09	**<0.001**
	No	36	95	2	1.98	38	18.91	
Regular follow-up rates	Yes	60	60	97	96.04	157	78.11	**<0.001**
	No	40	40	4	3.96	44	21.89	
Follow-up frequency	<1 month	20	57	15	14.85	35	17.41	**<0.001**
	1-2 month	40	34	78	77.23	118	58.71	
	2-6 month	10	59	7	6.93	17	8.46	
	>6 month	4	80	1	0.99	5	2.49	
	Unfollowed	26	26	0	0.00	26	12.94	
Drug use	No	29	29	65	64.36	94	46.77	**<0.05**
	Yes	71	71	36	35.64	107	53.23	
Drugs interacting with warfarin	NSAID	21	21	4	3.96	25	12.44	**<0.001**
	ASA	27	27	16	15.84	43	21.39	>0.05
	Amiodarone	10	10	2	1.98	12	5.97	**<0.05**
Presence of Comorbid Diseases	Available	97	98.1	87	86.14	184	91.54	**0.006**
	Unavailable	3	1.9	14	13.86	17	8.46	
Comorbid diseases	Diabetes Mellitus	13	8.1	22	21.78	35	17.41	**0.002**
	Hypertension	63	39.1	64	63.37	127	63.18	
	Heart disease	58	36	58	57.43	116	57.71	
	Chronic kidney failure	6	3.7	2	1.98	8	3.98	
	Chronic liver disease	2	1.2	1	0.99	3	1.49	
	Malignancy	10	6.2	0	0.00	16	7.96	
	COPD	6	3.7	3	2.97	9	4.48	
Stroke History	Available	23	23	56	55.45	79	39.30	**<0.001**
	Unavailable	77	77	45	44.55	122	60.70	

[a]: Pearson Chi-Square Test; NSAID: Nonsteroidal anti-inflammatory drug; ASA: Acetylsalicylic acid, COPD: Chronic obstructive pulmonary disease.

Table 3. Distribution of the bleeding site of the patient group (n=100)

The bleeding site	**n (%)**	
Upper gastrointestinal bleeding	39 (39)	**p<0.001**
Hematuria	14 (14)	
Lower gastrointestinal bleeding	3 (3)	
Nose bleeding	4 (4)	
Mucosal bleeding	4 (4)	
Subcutaneous hematoma, ecchymosis	6 (6)	
Intramuscular or intra-abdominal hematoma	3 (3)	
Hemoptysis	2 (2)	
Intracranial bleeding	3 (3)	
Other multiple, double, or triple bleedings	22 (22)	
Total	100 (100)	

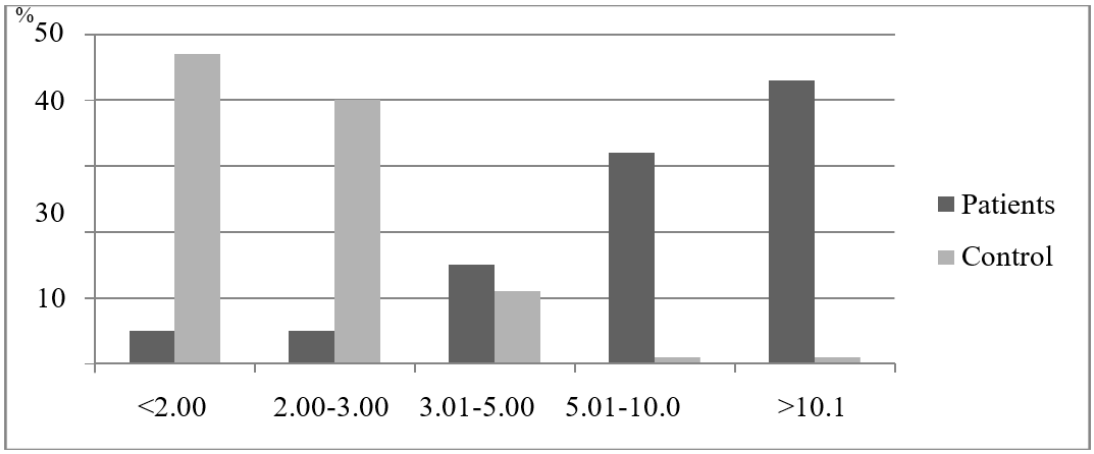

Figure 1. International normalization ratio distribution rate of patients and control group

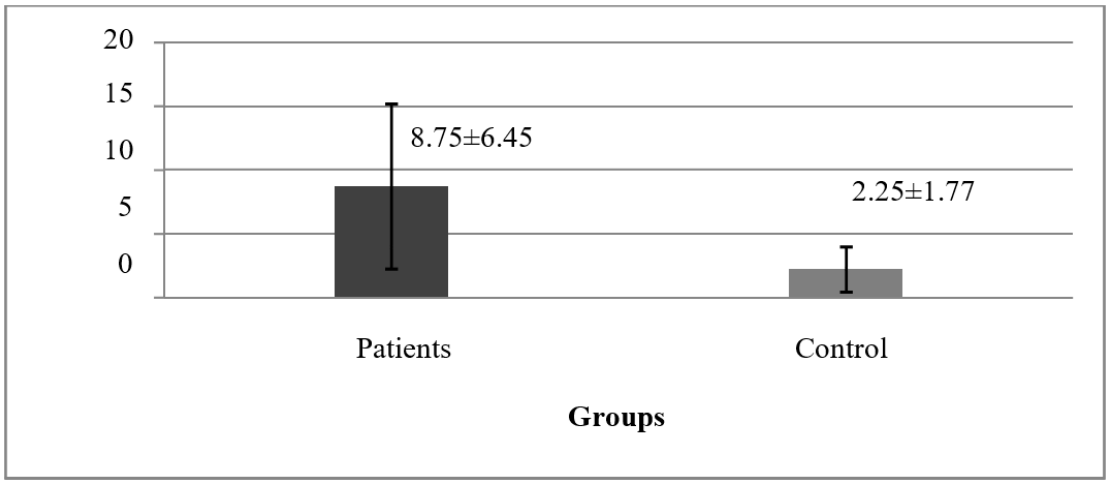

Figure 2. Mean international normalization ratio of patients and control groups values

Discussion

As known, the most substantial complication limiting the use of warfarin is bleeding. Physicians prescribe medicine for both short and long-term anticoagulation indications, but because of fear of bleeding and predictions of insufficient monitoring, patients cannot use it. We thought that our study would have an important place in daily medical practice besides its academic importance. At the end of this study, we determined the risk factors for bleeding and tried to create a risk classification system and compare it with the recent ones. For this purpose, we focused on age, sex, occupation, education, comorbid diseases, drug, stroke history, and patient follow-up.

Being 65 years old or older is a known risk factor that aggravates bleeding risk due to warfarin. In a study of 565 patients by Landefeld, it was found that elderly patients had a 3.2 times greater risk of major bleeding.[6] In the study of Beyth et al., it was found that being 65 years and older has a 2.7-fold risk of bleeding.[9] In the study of Shireman et al., it was determined that patients with AF aged 70 and over were at high risk, and it was found that being 70 years and older had a 1.63 times higher risk of bleeding.[10] In the study of Fihn et al., it was found that the risk of bleeding increased 1.10 times over the age of 80 years.[11] In the study of Wallvik et al., the risk of bleeding was 2.9 times increased in patients aged 60-69, 4.8 times in patients aged 70-79, and 6.6 times increased in patients aged 80 and over.[12] We conducted this study inspired by the study of Landefeld, who took 65 years and over as the risk group in terms of age. Older age was identified as a risk factor in Cox regression analysis, and over 65 years of age increased the risk of bleeding by 2.8 times. So our data also support the literature. For this reason, we believe that physicians who are considering prescribing warfarin should consider this situation and provide follow-up and information to the elderly group.

Gender is very substantial in the pharmacokinetic and pharmacodynamic effects of drugs. The incidence of side effects of some drugs varies according to gender. The decrease in oxidation by cytochrome p450 enzymes occurs more in men than in women. It is often claimed that women are more sensitive to certain medicines.[13] The role of gender in the bleeding complications of warfarin is controversial. In this study, we have not detected the effect of gender on bleeding. Studies emphasizing the existence of male or female superiority or that gender does not matter, [14–16] some studies have argued that the female gender increases the risk of bleeding[10,17,18] while some studies have reported that the male gender increases the risk of bleeding.[19,20]

It was emphasized that warfarin use, follow-up, and education level were important in the occurrence of bleeding complications.

Illiteracy, which was not statistically significant, was higher in the patients' group. Although there was a statistically significant difference between the groups, the level of education was not found as a risk factor in

the Cox regression analysis. Using a drug that is affected by many conditions of metabolism, such as warfarin, requires a certain intellectual level. Therefore, it is clear that illiteracy or a low academic level will increase the risk of bleeding. The reason that we have not been able to define this variable as a risk factor can be related to the low number of cases. We think that literacy, which is a parameter that cannot be considered in the patient group using warfarin, is a point to be considered with these data.

This study's results emphasize a situation. Approximately half of the participants in the control group had an INR value of less than 2, which might be suggested that they do not take warfarin. The same situation is observed in the whole world. Even though the INR controls were well monitored in multicentric randomized trials, in real life, this rate did not exceed 77% even in Sweden, where the best follow-up program is existing[21] In a study by Kalra et al., the rate of patients with INR <2.00 was 25%, the rate of patients with 2.0-3.0 was 66%, the rate of patients with INR >3.00 was > 9%.[22] In daily practice, the rate of patients with INR <2.0 is 26%, the rate of patients with 2.0-3.0 was 61%, and the rate of patients with INR >3.0 was 13%. As can be understood from these rates, reaching the target INR value is an unsolvable problem in the world.

The levels in the control group were found to be compatible with the average world levels. Reaching the target INR level in a warfarin-prescribed patient is never close to 100%. Below the therapeutic range, these patients are at risk of thromboembolic events even though they are on medication; there is a need for appropriate responsive drugs at fixed doses.

There was a significant difference between the patient and the control group in whether the follow-up was performed at a single center. In a study performed by Matchar DB et al., a comparison was made between the self-INR follow-up of a group of patients and INR follow-up in the clinic.[23] No difference was found between the two approaches in terms of reduced stroke risk, death, and major bleeding rates. Only minor bleeding rates increased. Based on these results, we believe that a warfarin-prescribed patient must be in follow-up for INR at a single center to reduce the patient's risk of bleeding. The adherence of patients to follow-up may be increased through self-monitoring.

Another important factor for holding the INR levels in the therapeutic ranges is regular INR monitoring. Frequent and regular follow-ups will prevent bleeding complications. The national guide recommends monitoring every 3-4 weeks.[24] The rate of regular follow-up was 96% in our non-bleeding control group and 60% in the patient group. This result is parallel with the hypothesis that the regularity of INR monitoring reduces the risk of bleeding.

In the analysis of the follow-up interval comparison of the patient and control groups, we found a result against the patient group, especially between the 1-2-month follow-up interval and non-follow-up. This situation leads

us to the opinion that not exceeding the follow-up period of 4-8 weeks may be a precaution to prevent possible bleeding.

Warfarin users are generally elderly patients, and since comorbidities are common in this group, they use multiple drugs. Therefore, we investigated the rate of drug consumption interacting with warfarin (Acetylsalicylic acid (ASA), Nonsteroidal anti-inflammatory drug (NSAID), amiodarone, e.g.). We found that this type of drug use was higher in the patient group. In the study of Zhang, in the concomitant use of warfarin and cephalosporins, an increased prevalence of bleeding was determined in comparison with the single use of warfarin.[25] However, a similar association was not detected in the association with NSAID/cyclooxygenase-2 inhibitors, amiodarone, and fenofibrate. In our study, the rate of NSAID and amiodarone usage in the patients' group was higher than in the control group. Especially randomly used ASA and NSAID drugs are commonly prescribed drugs that increase the risk of warfarin-associated bleeding. We recommend avoidance of usage of these drugs as much as possible, and if the administration is obligatory, the frequency of INR follow-up should be increased, and the patient must be informed about it.

The most common bleeding site was the upper gastrointestinal system. It should be noted that the most common bleeding site in warfarin users is GIS, and daily fecal control should be recommended for melena-hematochezia.

When the ratio of comorbid diseases was compared in the patients and control groups, comorbid disease rates were higher in the patient group. In this study, we found that the presence of comorbid disease increased the risk of 5.6-fold bleeding. The most common comorbidities in the study of Shireman et al. were hypertension and heart disease.[10] The most common comorbidities in this study were hypertension, heart disease, and diabetes. The reason why the group of patients with the comorbid disease is riskier for bleeding might be the use of multiple drugs and drug interactions, so these patients should be adequately informed and monitored at regular intervals.

When the stroke history was compared between the groups, we found that the stroke rate was higher in the control group. In our study, we found that the presence of a stroke history increased the risk of major bleeding 3.2-fold. Landefeld et al. Also found that stroke history increased the risk of major bleeding.[5] Patients with a history of stroke should be considered risky in terms of major bleeding.

As a result, it should be noted that the group of patients with long-term anticoagulation indications will face some problems. In addition to changing the standard of living of the patient and the habit of going to the physician, physicians need to give enough time to this patient group and inform the patients. The most important limitations of warfarin are metabolism and frequent laboratory monitoring. Anticoagulant drugs, which are effective in long-term anticoagulation and do not require laboratory monitoring and do not have

drug-nutrient interaction, have revolutionized this field. In fact, oral direct thrombin inhibitors and factor Xa inhibitors have been used in this field, and oral direct antithrombin inhibitor has been indicated for use in AF and ischemic stroke prophylaxis. In these circumstances, the throne of the warfarin was shaken. However, in indications such as prosthesis heart valve and childhood thrombosis, warfarin remains a gold standard treatment option.

The limitation of the study was that the sample group was smaller than other similar studies.

Ethical Considerations: The University Medical Faculty Ethics Board approved the study. (Number: 2008/101).

Conflict of Interest: The authors declare no conflict of interest.

[This study was presented as an oral presentation at the Turkish National Hematology Congress in 2011.]

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Case Report

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PAROXYSMAL TONIC UPGAZE MIMICKING INFANTILE SEIZURE

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Abstract

Non-epileptic paroxysmal events are very important in daily clinical practice. Paroxysmal tonic upgaze is a rare neuro-ophthalmologic non-epileptic paroxysmal condition characterized by episodes of continuous conjugated upward deviation of the eyes and normal horizontal gaze. Its pathogenesis is unknown, and its etiology is heterogeneous. The prognosis is often benign, but it's often confused with epilepsy. We present a case of "paroxysmal tonic upgaze" with a benign clinical course and spontaneous remission.

Keywords: Pediatric, non-epileptic, paroxysmal tonic upgaze.

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Introduction

Paroxysmal tonic upgaze (PTU) of childhood is a very rare neuro-ophthalmologic syndrome characterized by short-term episodes of upward deviation of the eyes. The age of onset varies between 1 month and two years. PTU is characterized by conjugated upward gaze attacks and accompanying neck flexion (chin down) to compensate for upward gaze. [1,2]

The diurnal course of the attacks and their disappearance during sleep, and the preservation of consciousness are very important for the differential diagnosis of epilepsy. In some cases, ataxia and developmental delay may accompany them. The pathophysiology of PTU is not clearly understood: genetic predisposition, immunological causes, dorsal brain stem immaturity, and depletion of neurotransmitters are considered as reasons.[1,3] Electroencephalography (EEG), cranial imaging and laboratory tests of the patients are normal. However, some studies suggest further examinations for patients with neurological symptoms such as developmental delay, nystagmus, and abnormal magnetic resonance imaging.[2,4,5]

In this article, we aimed to present a case of PTU, which is a rare, benign condition with a post-infectious cause.

Case Report

A 6-month-old female patient applied to the health institution with recurrent attacks accompanied by a sudden upward gaze in the eyes and neck flexion, which started two weeks after treatment for the diagnosis of bronchiolitis due to cough and fever complaints that started 20 days ago (Figure 1). She was referred to our clinic with the suspicion of epilepsy, as the attacks continued increasingly during the day. It was stated that the patient was full-term born with a normal delivery as the first child of the family. A history of phototherapy due to jaundice in the neonatal period was stated in the history. The patient's mental motor development was normal. Her parents were not relatives, and her cousin had a diagnosis of epilepsy.

The episodes, which did not exceed 20 seconds, started two days before her application, and their frequency has gradually increased. There was no change in consciousness during the attacks, and it was described that these attacks disappeared during sleep. On physical examination of the patient, growth parameters were in the normal percentile range. Neurological examination, including cranial nerves, ophthalmological examination and other system examinations, were normal. She had no nystagmus or ataxia during the attacks. Complete blood count, thyroid function tests, vitamin B12, folate, iron, iron-binding capacity and biochemistry parameters were normal. No seropositivity was detected in the viral panel. EEG and brain magnetic resonance studies were normal. During the follow-up, the number and duration of the attacks decreased without

treatment and decreased significantly after the seventh day. Attacks were rarely described in the first month of follow-up.

Figure 1. Upward gaze in the eyes of the patient at the time of admission.

Discussion

Paroxysmal tonic upgaze of childhood was first described as a benign disease by Ouvrier and Billson in 1988. The age of onset of PTU ranges from 1 week to 90 months. [1,3,4] Our patient was six month-old and had normal neuromotor development.

Although the pathophysiology is not clearly known, the condition is often not observed by means of tests such as physical examination, neuroimaging, and EEG. It is thought that conditions such as mutations like CACNA1A, immunological events such as vaccination and inflammatory diseases, vitamin B12 deficiency and immaturity of the central nervous system alone or together cause PTU. It has been reported that attacks increase in stressful conditions such as inflammatory disease, fatigue, and constipation. [2,5,6] In addition, the duration and frequency of attacks also vary. The attacks gradually decrease and disappear, and Verrotti et al. reported in their study that tonic upgaze attacks disappeared between 1 and 4 years without any treatment and without any change in psychomotor development. Attacks may increase in cases of stress, such as inflammatory diseases, insomnia, and fatigue. It is seen that many patients recover spontaneously at preschool age without the need for treatment and without causing any neuromotor developmental delay. However, mild learning difficulties were reported in some cases, and severe learning difficulties were reported in up to 40%. [4,7] In our patient, the attacks started after bronchiolitis and varied during the day. Her neuromotor development was

normal, and EEG and brain MRI showed no abnormalities. The complaints disappeared with sleep and regressed over time without treatment. Neuromotor development was normal.

Some treatment regimens, such as antiepileptic agents and levodopa, have been suggested. A noticeable recovery has been noted in some patients using levodopa, but the benefit of antiepileptic drugs has not been demonstrated. However, levodopa therapy is not routinely recommended. In patients with low vitamin B12 levels, regression has been reported in complaints with vitamin B12 supplementation. It has been demonstrated that carbonic anhydrase inhibitors are effective in patients with CACNA1A mutations.[4,6-8] Recovery was observed in our patient without the need for any treatment, and it was observed that the complaints disappeared with the regression of the immunological status.

Since there was no structural lesion or any cause, such as vaccination, the patient we presented was considered a post-infectious paroxysmal tonic upgaze. In conclusion, PTU is a transient, benign condition that is extremely rare in childhood. It is very important since epilepsy is included in the differential diagnosis and is rarely seen.

Ethical Considerations: Informed consent has been obtained from the parents of the patient.

Conflict of Interest: The authors declare no conflict of interest.

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Review

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A NEW CONCEPT IN PROTECTIVE HEALTHCARE: QUINARY PREVENTION

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Abstract

Quinary Prevention; It is a set of policies, conditions, actions and measures aimed at reducing the risks associated with disseminating inappropriate health-related information and minimizing the impact of such misinformation on the progression or development of diseases. Quinary Prevention is under the multi-layered responsibility of health professionals, professional organizations and legislators. Legislators should prepare laws/regulations to prevent and deter the spread of health-related misinformation. Health service providers should assume the primary responsibility of Quinary Prevention, constantly update themselves in the discipline they choose, disseminate correct information and increase health literacy, inform the public through professional organizations or sites where relevant experts are the controllers, and report those who share false information to the necessary authorities. The public should not blindly believe every information conveyed through social media and should consult a healthcare professional. In social media, the impact of which is increasing day by day, the legal infrastructure should be prepared for an accurate information presentation by taking the necessary precautions, and health service providers, who are experts in their work, should contribute to the health literacy of the public by providing information on these platforms. Family physicians, who provide preventive and curative health services together, must know the protection steps within the scope of preventive medicine and update themselves in this regard. In this context, 'Quinary Prevention', the newest preventive care steps, was mentioned to guide health service providers, especially family physicians.

Keywords: Quinary Prevention, preventive medicine, family practice, disinformation, information hygiene, infodemic.

Introduction

While WONCA Europe defined Family Medicine, it emphasized that it is an academic and scientific discipline with unique educational content, research, evidence base and clinical practice. It has been emphasized that Family Physicians are personal physicians trained in this discipline and are responsible for providing continuous and comprehensive care to all those seeking medical care regardless of age, gender and illness. One of the most critical components of this care is the improvement of the patient's health and well-being through effective and appropriate interventions. In this context, curative and preventive health services are offered together.[1]

Although preventive health services for the individual and society are among the daily routine work of family physicians, protection, with its broad definition, is a set of actions aimed at preventing, eradicating, eradicating or minimizing the effect of the disease or, if neither, slowing the progression.[2]

Family physicians, who provide preventive and curative health services together, must know the protection steps within the scope of preventive treatment, benefit from them while providing preventive health services, and update themselves in this regard. This review is planned to discuss Quinary Prevention, the newest preventive care step, to guide health service providers, especially family physicians.

Traditional Prevention Steps

Primary, secondary and tertiary protection, the three main steps of preventive health services, are aimed at the person.[2,3] Primary prevention is the measures applied to the disease or disease groups to prevent the disease from the beginning and reduce the incidence of diseases. Providing clean water and food and routine vaccination programs are examples of this. Secondary prevention, defined as early diagnosis interventions, includes activities to recognize the disease while symptomatic and control its progression. Screening programs for breast, colorectal, and cervical cancer are examples of this. In tertiary prevention, the condition is diagnosed. Still, the aim is to protect and increase the functionality and quality of life affected by the disease and reduce possible complications by providing services such as treatment and rehabilitation to increase life expectancy. An example of this is the administration of aspirin, beta-blockers, and statins at discharge to patients whose hospital treatment has been completed with the diagnosis of acute myocardial infarction.[4–7]

Primordial protection, under the umbrella of primary protection, is a combination of measures and actions aimed at preventing the conditions that cause the disease to predispose to social and environmental conditions and aiming to reduce or eliminate the occurrence of risk factors. For example, smallpox has been completely eradicated, and primordial protection has been provided, thanks to the effective vaccination program, and the

disease is no longer a risk factor for society. Efforts in this protection are directed to individuals who are not yet at risk and before risky situations occur. These efforts are often carried out through personal or mass training.[2,3,8,9]

While the principle of 'first do not harm', one of the essential principles of medical education, emphasizes the importance of protection, quaternary protection is a new term used for this old concept.[10] In addition to interpreting the normal and physiological conditions as pathological conditions, which is defined as medicalization, it also prevents the patient from unwanted conditions such as over-diagnosis and over-treatment that do not contribute to the patient's quality of life and life span (sometimes even have a negative effect) and society, and to provide them with scientific, cost-effective and ethically acceptable care.[4,5,11] Jamoulle stated that the most challenging protection step of the physician is quaternary protection. At this step, the physician can learn the patient's underlying anxiety with patient-centered and history-based medicine approaches.[3,11–13] Quaternary prevention can be applied in all areas of health care, and it is scientifically acceptable, ethically appropriate and appropriate to provide patient care with the highest quality and with the least number of interventional procedures, avoiding unproven screenings, inappropriate antibiotic use, off-label and unnecessary drug use, incorrect rehabilitation methods. Recommends medical care tailored to patients' needs.[14–19] Traditional Preventive Medicine Steps are summarised in Table 1.

Table 1. Traditional Preventive Medicine Steps

Prevention Steps	Definition
Primordial Prevention	Considered a subset of primary prevention, it generally refers to taking preventive measures and eliminating risk in the absence of risk factors in the population.
Primary Prevention	It refers to the preventive measures taken in the absence of the disease in people with risk factors.
Secondary Prevention	It refers to taking measures for early detection and treatment of the disease to prevent complications.
Tertiary Prevention	It refers to the strategies applied to minimize the deterioration of health due to complications caused by diagnosed diseases and to prevent their worsening.
Quaternary Prevention	It refers to overdiagnosis, over-labeling (stigmatization), the medicalization of standard conditions (medicalization) and preventive measures from overtreatment.

THE NEW DIRECTION OF PROTECTION: QUINARY PREVENTION

The Cause and Story of the Concept's Emergence

Thanks to technological developments and advances, communication tools have improved in recent years. This has helped health services be more efficient and effective by providing fast transmission of information. However, this has also facilitated the spread of false information and has had potentially harmful effects on health, so the impact of inaccurate or false information has had an impact on all levels of protection.[20] Using technological communication tools to spread misinformation about health is an e-hearsay.[21] The hearsay or false information sources are traditional media, primarily social media, websites for education/health services, messages transmitted via mobile phones, and consumer marketing.[20]

Preventing the spread of misinformation about health or health precautions or the effects of disseminated misinformation has gained importance in today's high-tech environment. To represent this idea scientifically, it was necessary to define it in an appropriate conceptual framework and to produce the proper term. To create a new term suitable for this level of protection/prevention, researchers searched various English words and searched for words related to 'five' and 'protection' in these dictionaries. The expression "Quinary" is derived from the Latin word "quinarus" for the number five and describes the fifth object in a sequence or an arrangement of five. Since the fourth step, the conceptual framework for the traditional protection steps was defined last, this newest step was 'Quinary Prevention'.[22–24] During the creation of this new term, care was taken to meet the international standards envisaged in its definition and conceptualization.[25] The five protection steps were formed by adding Quinary Prevention to the traditional protection steps (Figure 1).

Definition and Concept

Preventing the dissemination or the effects of false health and/or health precautions is important in today's digital environment, which allows rapid and widespread dissemination of (false) information.[26] In addition, the fact that the Coronavirus Disease (COVID-19), which started in Wuhan, China, in December 2019, spread rapidly around the world with a wave of fear, prejudice and erroneous information, and triggered discrimination and stigmatization with the failure of intervention policies, the World Health Organization (WHO)) has caused this situation to be called "Infodemia". With this situation, preventing the spread of misinformation or its effects on health has become even more critical.[27]

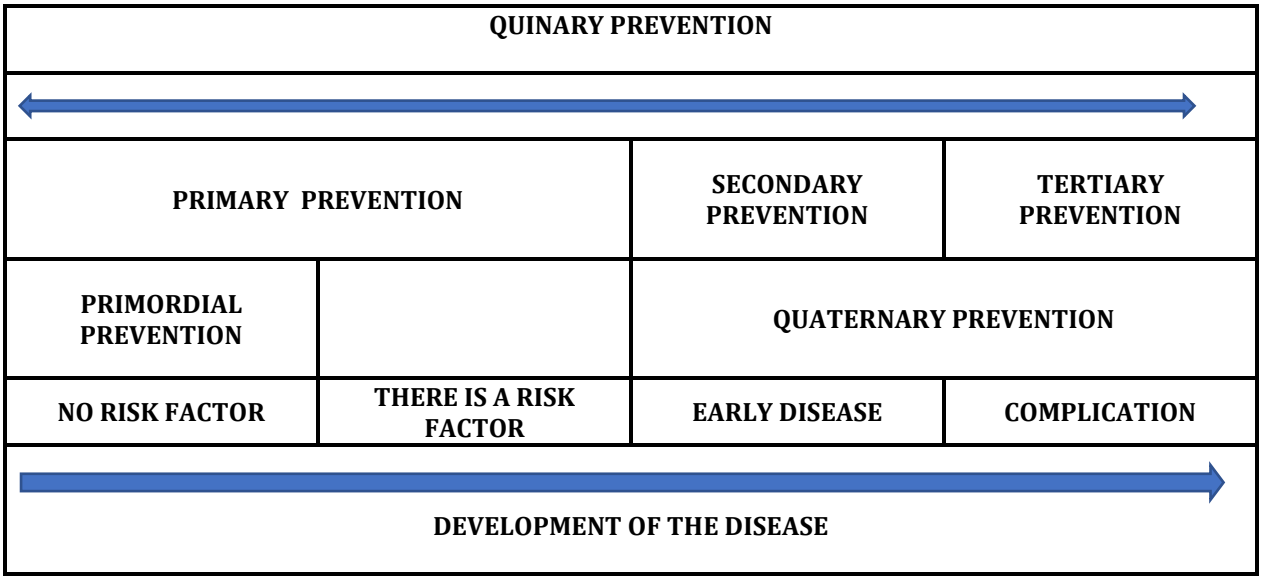

Figure 1. Scope of Quinary Prevention and Distribution of Various Protection Levels by Disease Development.[20]

Quinary Prevention; A set of policies, conditions, actions and measures aimed at minimizing the risk of transmitting inappropriate information regarding health maintenance, disease prevention or disease management and the impact of such misinformation on the progression or development of diseases. However, factors or actions that hinder developments and advances in modern technology, such as blocking or limiting mass communication, are not considered within the scope of finite protection because they also prevent the dissemination of useful information.[20] Quinary Prevention, by definition, overlaps with and includes other protection steps (Figure 1). Quinary Prevention is the way to avoid false health information or to prevent the adverse effects of false information on the health of individuals. Therefore, if Quinary Prevention is applied correctly, it will be easier for the other protection steps to be practical.

Scope of Quinary Prevention

Conditions that spread false health information, such as e-gossip, constitute an obstacle to disease care in many areas, such as diabetes, atrial fibrillation, and obesity-bariatric surgery.[21,26,28–30] With the power of multimedia, every individual has become a publisher. This power should also be used in disseminating correct information and overcoming these obstacles. Examples of situations where this power is used can be given as examples for Diabetes Mellitus disease, Indian endocrinologists directing the public to diabetes care centers using WhatsApp and Twitter, non-governmental organizations organizing systematic campaigns on social media, and religious leaders in Bangladesh raising awareness about gestational diabetes mellitus through social media.[21] Another example is fighting with popular myths within the scope of Quinary Prevention regarding Atrial Fibrillation

and sharing the correct versions of wrongly known situations on social media.[28] On the other hand, misinformation about obesity and obesity surgery (bariatric surgery) affects people in two ways, causing people who are ideal for surgery to give up on surgery or because it is used in treating Type 2 Diabetes Mellitus. However, there is little data about it; people who are not ideal for surgery have surgery. Another example is sharing misconceptions about this situation and simple ways to counter them.[29] On the other hand, in an article dealing with the parenting relationship with Quinary Prevention, misinformation that impacts parenting and its effects on children's health was mentioned since parenting is considered a health determinant that affects processes such as neurodevelopment, attachment, and stress response.[26,31,32] Although Quinary Prevention is a new concept, it is also important in fighting and preventing cancer. The fact that this concept is included in the website of the Cancer Prevention Research Group operating in Greece is one of the indicators of this situation.[33] Kalra et al. The mention of Quinary Prevention in a study conducted by Dr. et al. in which euthyroidism was discussed from a biopsychosocial perspective in thyroid diseases proves that this concept has started to gain ground in the endocrinology community.[20,34,35]

Information Hygiene and Quinary Prevention in False Information, Disinformation and Infodemic

Incorrect information is defined as "misleading" information in the literature and is generally evaluated as "an ill-intentioned error" .[36,37] disinformation, on the other hand, is false information deliberately spread to deceive and/or deceive.[38,39] In addition, after the emergence of COVID-19 in 2019, as the world became aware of this new disease, misinformation and disinformation spread through the internet and social media. This condition, which indicates the presence of the disease, is called "Infodemia".[27] The concept of "Information Hygiene", expressed as a set of requirements and practices that help protect and obtain health information and prevent the spread of misinformation about health, has gained importance together with the concepts of misinformation, disinformation and infodemic.[40] Scientifically correct and acceptable information is essential, and the information circulating among the public should minimize unintentional negative information because misinformation can lead to stigma and panic. In this context, it is important to ensure that Information Hygiene protects the public from false information, and the measures and actions to be taken in this area are important.[40–42] In this context, four basic methods have been mentioned in the fight against infodemic, and these are Information Monitoring (Infovenance), building e-Health and Science Literacy capacity, promoting information improvement and quality improvement processes, and accurate and timely information translation by minimizing political and commercial factors.[43, 44]

It has been shown that the use of social media increases significantly in emergencies such as COVID-19, natural disasters and crises.[39,42,45] In this context, a new information platform called WHO Epidemic Information Network (EPI-WIN) was launched to share tailored information with specific target groups immediately after

COVID-19 was declared a Public Health Emergency of International Concern by the WHO risk communication team.[44]

To prevent disinformation, detecting texts on the internet is of great importance. For this, "Threat Modeling", a widely used technique in the field of cyber security, has been developed, but it is seen that its full potential has not been utilized.[39] In this regard, Zellers et al., there is a Disinformation Threat Modeling study carried out, and the lack of much work on this modeling in the literature supports this situation.[46] With "Threat Modeling", the contents such as text, pictures and videos that create disinformation can be detected through existing databases, and moves can be produced to prevent them.[39]

There is usually underlying miscommunication and distrust based on disinformation and infodemic, and healthcare professionals should be informed of situations that may create disinformation to prevent disinformation, misinformation and infodemic, and health communicators should work to inform practitioners about the most common or dangerous narratives their patients are exposed to. Through intense disinformation reviews published periodically, academic and health education workshops should be organized. Healthcare policymakers should include education and training materials so that healthcare providers can better communicate with their patients when exposed to disinformation.[47]

Responsibilities in Quinary Prevention

The collective and concerted efforts of healthcare providers, the public and law enforcement can prevent misinformation. Quinary Prevention is under the multi-layered responsibility of health professionals, professional organizations and legislators.[26]

Legislators

In this part of Quinary Prevention, the responsibility belongs to more than one stakeholder, and the suggestions are as follows:[20]

Legislators should prepare laws/regulations to prevent and deter the spread of health-related misinformation. These regulations should cover all social media (including Facebook, Twitter and WhatsApp) and mass media (print, radio and television). In addition, it is emphasized that introducing these regulations should be deterrent and strict.[26]

The Ministry of Health should campaign to spread salutogenic (promoting physical and mental health of individuals/communities) messages in society.

Administrators of social platforms should also take the responsibility of moderating and, if necessary, censoring posts that are wrong about health and could harm public or individual health. Both administrators and legislators should work closely with healthcare professionals and information technology professionals.

In all these studies, it is essential to make clear, up-to-date and accurate information accessible through reliable sources, preferably two-way communication, by addressing the uncertainties. The importance of including Quinary Prevention in the process should be emphasized when planning health interventions.

Healthcare Providers

Within the scope of Quinary Prevention, healthcare providers can provide information on self-management and care of diseases on social media. Health service providers should assume the main responsibility of Quinary Prevention, should constantly update themselves in the discipline they choose, disseminate correct information and health literacy, inform the public through professional organizations or sites where relevant experts are the controllers, and report those who share false information to the necessary authorities.[20,26]

Healthcare providers can actively contribute to the general care of diseases by harnessing the power of social media platforms by providing sick people access to accurate information.[48] Nelakurthi et al. The study conducted on Diabetes Mellitus, which was achieved through web-based and in-clinic surveys, showed that patients with Diabetes Mellitus who regularly use social media improved their adherence to lifestyle change recommendations.[49] In a study by Abedin et al., in which they identified 16 Facebook groups with a total of 103 relevant posts on diabetic foot care on Facebook, it was reported that 45.6% of the posts were useful, and Facebook was a valuable platform for sharing information about diabetes care.[50] From this point of view, it can be thought that the benefit of this and similar platforms can be further improved if healthcare providers disseminate useful and original information about treating chronic diseases such as diabetes care.

Healthcare providers should also refrain from commenting on situations they are unfamiliar with or not competent to discuss. In cases with potential resistance to preventive and control measures, professionals trusted by society should be identified and informed through these people. To ensure that long-term interventions are contextually and logically appropriate and disseminated to the community, plans can be made on how individuals' health information will be used, and additional arrangements can be planned.[20]

Health professionals can participate in user-friendly patient information sites prepared by professional organizations by being involved in decision-making. They may also advocate for health through health talks, blogs, and discussion programs.[30]

Family Physicians as Healthcare Providers

Preventive health services for individuals and populations are among the daily routine task of family physicians.[10] They are personal doctors, primarily responsible for providing comprehensive and continuing care to every individual seeking medical care irrespective of age, sex and illness. One of the most critical components of this care is the improvement of the patient's health and well-being through effective and appropriate interventions.[1]

Quinary prevention means preventing health-related hearsay or misinformation or its ill effects on the health of individuals.[22-24] Within the scope of protection in negotiating management plans with patients, Family Physicians integrate physical, psychological, social, cultural and existential factors, utilizing the knowledge and trust engendered by repeated contacts.[1,2] For this reason, it is crucial for family physicians who provide preventive and curative health services together to know the protection steps within the scope of preventive treatment, benefit from them while providing preventive health services, and update themselves on this issue.

Public

Health professionals, legislators, and the public are responsible for achieving ideal health. As with other protection steps, it is generally the duty of the public in Quinary Prevention. In this context, ensuring that the public can distinguish between true and false information through ongoing information campaigns is necessary. To achieve this, the individuals who make up the public should be technically and socially competent, and their health literacy should be developed.[20] The public should not blindly believe every information conveyed through social media and should consult a healthcare professional to confirm this information.[26]

In Canada, Leong et al. reported in a study that 32.4% of YouTube videos were misleading, and it was stated that misleading videos were more popular.[51] The fact that misleading videos are more popular indicates the public's tendency in this regard. Public awareness should be created to correct this situation and raise health awareness.

A study on 56 children and teenagers revealed that regular Facebook and Skype use improved people's knowledge and helped them cope better with their illnesses.[52] This study shows that the impact of technological opportunities such as social media on children and young people is essential. It should be considered that this effect is more important in Turkey, where the majority of the population is children and youth. The interventions should be made by considering children and young people.

Some herbal, chemical, and physical treatments and methods, which can be presented as an alternative to evidence-based medicine and generally shown as pure and harmless, can spread rapidly through the media and cause undesirable results.[30,52] It should be remembered that such treatments and methods, which are not evidence-based, should be evaluated within the scope of Quinary Prevention.

Conclusion

Quinary Prevention is critical in preventing the spread of false and hearsay information about diseases. All healthcare providers, especially family physicians, who provide preventive and curative health services together, should apply Quinary Prevention and take an active role in preventing threats as a part of routine clinical practices by updating themselves. The legal infrastructure should be prepared for an accurate information presentation by taking the necessary precautions in social media, the impact of which is increasing daily.

Ethical considerations: Since public data and related literature were analyzed in our study, there was no ethical violation.

Conflict of Interest: The author declares no conflict of interest.

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LITERATURE REVIEW ON THE EFFECTIVENESS OF MEDICINAL LEECH THERAPY IN THE WOUND HEALING

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Abstract

Medical leech therapy, which has a history of thousands of years, is still the subject of many scientific studies today. These studies have shown that medicinal leech therapy has anticoagulant, antimicrobial, anti-inflammatory and analgesic effects, as well as increases blood flow in the bite area. Due to these stated effects of leech therapy, it has potential benefits for patients experiencing wounds of the skin and tissues. This review focused on presenting the studies in which medical leech therapy is used to promote wound healing, particularly in post-traumatic wounds and non-healing chronic wounds. Additionally, this review aims to recognize medicinal leech therapy, introduce the leech species that have therapeutic effects and indicate the effect mechanisms of leech saliva on wound healing. The case series, single case reports and review articles on the use of medicinal leech therapy in wound healing were inspected. The original animal-based studies on wound healing were also investigated in this review for additional information. Various reports indicate that medicinal leech therapy has potential benefits for patients experiencing venous congestion of the skin and tissues, as well as varied types of ulcers. Medicinal leech therapy has promising potential in the healing of post-traumatic and chronic non-healing wounds. Nevertheless, more studies are needed for the potential effects of medicinal leech therapy in wound healing should be clarified by further studies.

Keywords: Hirudotherapy, medicinal leech therapy, trauma, ulcers, wound healing.

Introduction

The skin, which is the largest organ of the body and surrounds the body as a barrier against the external environment, plays an active role both physically and immunologically. Along with these, the skin, which contains hair and nails, also has functions such as UV protection, hormone and enzyme production, homeostasis, and thermoregulation. [1] Wound healing is a physical process that is essential for preserving the integrity and function of the skin or tissue by eliminating the defects that occur after an accident, trauma, illness or surgery. Normal wound healing consists of three intertwined stages that cannot be separated from each other with clear lines. [2] The usual wound healing consists of three interlocking phases, which include the homeostasis/inflammatory phase, the proliferative phase, and the remodeling phase. [3] Although the wound healing stages after the surgery are similar to the others, the immune response and increased inflammation in the body may cause the wound healing to go beyond its normal course and be delayed. Therefore, the maintenance of wound healing is important. [4,5]

Leech therapy is one of the most effective and natural ways of wound healing with its mechanical and biochemical properties. Medicinal leech therapy can be used in post-traumatic wounds to increase tissue salvage in amputated tissue replantation or flap surgery. It can also be used for chronic non-healing wounds, such as for treating diabetic foot ulcers, pressure ulcers, and venous leg ulcers. [6] The fact that it is low cost, fast, effective, easy and practical makes medicinal leech therapy preferable.

Medicinal leech therapy, also known as *hirudotherapy,* is one of the rare complementary and traditional treatments in which invertebrates are used for medical purposes. The history of leech therapy goes back to 1500 BC, and the usage of leeches can be seen in the Ancient Egyptian Hieroglyphs. However, known written sources have reached this day from Nicander of Colophon in the first second-century BC. [7] Unani physicians, who believe that diseases in the body are caused by humoral imbalance, which is Galen's (130-201 AD) theory influenced by Hippocrates (460-370 BC), have used leech therapy for centuries. Avicenna also recommended leech therapy, especially for skin diseases, in his book *Canon of Medicine.* [8] The use of leeches for medicinal purposes continued increasingly until the 19th century when their excessive use was referred to as *leechmania*. The use of *Hirudo medicinalis* in Europe was so excessive that leeches of this species were in danger of extinction. Thus, regulations were created for the leech trade. Therefore, the demand for leech therapy decreased with the decreasing leech populations and the developing new treatment methods. [9] Afterwards, research on the content of leech saliva and the FDA's (United States Food and Drug Administration) approval in 2004 to use *Hirudo medicinalis* for therapeutic purposes in plastic and reconstructive surgery drew attention to hirudotherapy again. [10]

In Turkey, the 'Regulation on Traditional and Complementary Medicine Practices' was published in the Official Gazette dated 27.10.2014 and numbered 29158. Thus, criteria for the use of *H. medicinalis* and *H. verbana* for therapeutic purposes were determined. In this way, the way was opened for the use of leeches obtained from sterile medical leech farms approved by the Ministry of Agriculture by the relevant personnel and physicians in treatment and application centers for medical purposes. Leech therapy can be applied in government institutions as well as in approved private institutions. [11]

Hirudotherapy is defined as the use of sterilized medical leeches in the treatment. Medicinal leeches belong to the phylum Annelida, class Clitellata and subclass Hirudinea. [12] Leeches feed on the blood of their hosts, the main benefit of leech therapy is that they deliver various bioactive substances from their saliva into the host's bloodstream during sucking. [13] The main purpose of this study is to present the studies in which medicinal leech therapy is used in the treatment of wounds in the form of a review. Additionally, this study aims to recognize medicinal leech therapy, introduce the leech species, which have therapeutic effects and indicate the effect mechanisms of leech saliva on the wound healing.

Materials and Methods

There are various studies on medicinal leeches and medical leech therapy. These studies include *in vitro* cell culture studies [14] and *in vivo* animal studies, as well as case reports. Since medicinal leeches are used in the treatment of various diseases, we come across case reports for many diseases. In this context, there are researches in which medical leeches are used in various diseases such as rheumatic and joint diseases, hemorrhoids, injuries, and ulcers and also for cosmetic anti-aging purposes.

This is a literature review. The authors searched for data on the medicinal leech therapy published between January 2000 and July 2022. The PubMed, Science Direct, Scopus and Google Scholar databases were investigated. The literature on the effects of leech therapy on wound healing has been reviewed in detail. First, leech therapy and hirudotherapy words were used for searching. Additionally, the substances in the leech saliva that may be responsible for wound healing were also investigated. The keywords were searched with multiple electronic searching in abstracts and titles as follows: leech, leech therapy, hirudotherapy, wound healing, medicinal leech therapy, saliva, bioactivities, *Hirudo medicinalis*, *Hirudo verbena*, *Hirudo orientalis*, and *Hirudo manillensis*, chronic wounds, non-healing wounds, trauma.

Articles published before 2000, articles that are written in a language other than English, articles unopen to full access, articles that are out of the context of the research, the incompatibility of articles, articles with insufficient quality, or articles with similar studies excluded from the study.

After removing all articles except for articles on wound healing, 60 of these articles were published before 2000, 190 of them were not full text, 36 of them were not eligible, and 31 of them were duplicates; thus, they were excluded from the review. As a result, 12 articles were selected as case reports for this review (Case reports only, *in vitro* and *in vivo* studies not included in the number given).

Results

Leech Species with Therapeutic Effects

In leeches, the body is flattened dorso-ventrally. The segments are in the form of an anterior and posterior drawer. Their bodies always consist of a fixed number of 34 segments. In their mouths, there are 300 teeth in total, with floating pieces in each jaw. That's why their bites are Y-shaped. Leeches, which are extremely sensitive to sudden changes such as temperature and amount of chlorine in their living environment, die, especially despite high chlorine content. Leeches use oxygen dissolved in water or atmospheric oxygen by taking it from the body's surface. [15,16]

Although there are almost 800 leech species in the World, only about 15 of them can be classified as medicinal leeches. The types of medicinal leeches of subclass Hirudinea used for medical purposes are shown in Table 1. The leeches used for medicinal leech therapy generally belong to the genus Hirudo of the family Hirudinea. These leeches are accepted as non-poisonous and medicinal. One of the most important things in the choosing of leeches for medical purposes is that leeches should be sterile and not used on another person before. Additionally, only leeches in the medical leech category can be used for treatment.

The Effect Mechanisms of Medicinal Leeches

The therapeutic mechanisms of action of leeches have been extensively interpreted from the earliest times to the present day. Leech therapy includes an initial bite and a bonding period of about 20 to 45 min, during which the leech sucks blood. Formerly, it was believed that the main therapeutic benefits were from the phlebotomy when the feeding of leeches with the blood of their host, but in fact, it is shown the benefits caused by the bioactive substances found in the leech saliva that secreted into the host's bloodstream during sucking. [17] The bioactive compounds found in leech saliva and their functions are given in Table 2.

Table 1. The types of medicinal leeches most commonly used for medical purposes

Hirudinea	*Hirudo medicinalis*
	Hirudo verbana
	Hirudo orientalis
	Hirudo sulukii
	Hirudo nipponia
	Hirudo troctina

Leeches cling to their prey with their suction cups located in the head and tail regions of their body. When the leech begins to feed, it releases chemicals that expand the vessels and increase the fluidity of the blood and analgesics. After the leech bite, it creates a suction pathway (extracellular matrix degradation), inhibits adhesion, aggregation and coagulation (inhibition of platelet function and anticoagulant effect), increases blood flow, protects itself (antimicrobial activity) and avoids detection (analgesic and anti-inflammatory effects). [12] After the feeding period, the leeches drop out from the attachment area as a result of complete satiation. Within the digestive system of leeches, blood is protected by endoenzymes. Endosymbiotic bacteria such as *Aeromonas hydrophilave* and *Pseudomonas hirudinia* play a role in the digestion of blood after feeding and prevent its putrefaction. [18]

Although more than 100 bioactive substances in protein and peptide structures with different molecular masses have been observed in leech saliva, some with an important active role have been identified.

Animal-based Studies on the Effects of Medicinal Leeches on Wound Healing

Animal studies have investigated the effects of hirudotherapy on wound healing and flap survival in rats and mice. These studies showed that leeches decrease necrosis via increased blood flow in the bite area and increase wound healing and flap salvage.

In a study, the researchers investigated the effect of leech therapy and topical phenytoin (PHT) application on incisional skin wound healing in an animal model (Wistar albino). The wound healing process of the rats in the group treated with medical leech (*H. orientalis*) was significantly faster than that in the group treated with topical phenytoin (PHT). [24] In another study, the scientists conducted a study on the effectiveness of hirudotherapy and ischemic preconditioning in flaps exposed to ischemia for a long time in a mice model. Especially when the hirudotherapy group was compared with the control group, the rate of necrosis decreased satisfactorily, and the flap survival rate increased to an average of 88%. [25]

Table 2. The Bioactive Compounds Found in Leech Saliva and Their Functions. [12,19-23]

Modes of Action	Substance	Target or Function
Analgesic and Anti-İnflammatory Effects	Bdellins	Inhibits trypsin, plasmin, and sperm acrosin
	Hirustasin	Inhibits tissue (but not plasma) kallikrein
	LDTI (leech-derived tryptase inhibitor	Inhibits tryptase
	Eglins	Inhibits α-chymotrypsin, chymase, subtilisin, and the neutrophil proteinases elastase and cathepsin G
	LCI (leech carboxypeptidase Inhibitor	Inhibits Carboxypeptıdase A
	Complement C1 Inhibitor	It can bind to complement-fixing sites of antibodies (IgG and IgM)
	Guamerin from *Hirudo nipponia*	Inhibits Leukocyte-elastase specifically
	Piguamerin from *Hirudo nipponia*	Inhibits kallikrein, and trypsin
Anticoagulant Effects	Hirudin	Inhibits thrombin
	Factor Xa Inhibitor	Inhibits Factor Xa
	Destabilase	Dissolves stabilized fibrin
	Gelin	Inhibits elastase, cathepsin G, and chymotrypsin
Extracellular Matrix Degradation	Hyaluronidase	Targets endoglucoronidic linkages of hyaluronic acid
	Collagenase	Dissolves the collagen particles
Anti-Platelet Effects	Apyrase	Targets Adenosine 5' Diphosphate, arachidonic acid, platelet-activating factor (PAF), and epinephrine
	Calin	Inhibits collagen-induced platelet aggregation (directly) or von-Willebrand factor collagen binding (indirectly)
	Saratin	Inhibits the binding of α_2 integrin subunit I domain to collagen
The Effects on Blood Flow	Acetylcholine	Targets blood vessels
	Histamine-like Substances	Targets blood vessels
Antimicrobial Effects	Destabilase	The β1–4 bonds of the peptidoglycan layer in the bacterial cell wall
	Chloromycetin	Bacterial protein synthesis
	Theromacin	The bacterial membrane
	Theromyzin and Peptide B	-

The researchers investigated the effects of medical leech application on flap survival. They created ischemic random skin flaps on the rat dorsum. The study consisted of three groups: the control group, the group with one leech applied on the flap and the group with three leech-applied on the flap eight hours apart. While they found a significant decrease in flap survival in the group with three leech-applied flaps compared to the control, there was no significant difference between the group with one leech-applied flap and the control. [26]

Clinical Effects of the Medicinal Leech Therapy on Wound Healing

Post-traumatic Wounds

Some numbers of reports show the effectiveness of leech therapy on the salvage of organs damaged by traumatic injuries.

Leech therapy was applied to the patient with a laceration of the right ear after a vehicle accident to reduce venous congestion in this region. At the early stage of wound healing, the ear exhibited marked improvement, and signs of adequate revascularization began to appear in this area after the medicinal leech therapy. At the late stage of wound healing, the ear exhibited signs of complete revascularization. [27] When we look at the literature, there are various studies showing that medical leech therapy is used to salvage venous drainage in ear reconstruction. [28]

In one case, microsurgical lip replantation was performed on a female patient who had traumatic lip amputation because of a dog attack. After the signs of venous congestion in the lip area were observed on the first postoperative day, medical leech treatment was performed. Medicinal leech therapy supported venous drainage and revascularization in the replanted lip. As a result, lip replantation was successful without any complications. [29] In the literature search, there are many cases in which leech therapy is used for revascularization, wound healing and survival of the damaged lip and surrounding structures after traumatic injury. [30]

Flaps, which are one of the reconstructive procedures used to close soft tissue defects formed for any reason, are also generally used for post-traumatic wounds.

In a case report, a nasal flap was applied to a patient who had a nasal laceration after a weapon injury. Medical leech therapy, once daily for five days, was applied to increase flap survival in the patient who showed signs of venous congestion after the operation. Although revision surgery has been recommended after the scar tissue has matured, the fact that the flap remains infection-free and viable during the treatment, thanks to leech therapy, has been considered quite positive for the researchers. [31]

Because of crushing, the fingers of the 25-year-old patient, whose three fingers were at the level of rupture, were surgically replanted in place. Leech therapy, a total of 15 leeches, was applied to the patient to increase blood circulation in the finger area. The result was gratifying. Venous congestion decreased thanks to leech therapy. On the seventh day after the operation, the patient lost the fifth finger, but the third and fourth fingers were salvaged. The patient was able to return to work after three months. [32]

Medical leeches were applied for treating ring avulsion in two cases, in which the arterial circulation was healthy, but only the venous supply was impaired. These cases were treated successfully with leeches, in addition to micro venous reconstruction was achieved by means of leech therapy. [33]

In a case series evaluating the efficacy of Leech Therapy, patients with traumatic Soft Tissue Avulsions were included in this study. Medical leech therapy was applied to four patients after reconstruction and microvascular flap. Their study confirmed the excellent and positive effects on healing after medical leech therapy for flaps in the case of venous congestion. Additionally, the researchers stated that medicinal leeches might play a critical role in salvaging the soft tissue segment in such cases. [34]

When we look at the literature, it is possible to come across studies in which the positive effects of medical leech application on patients suffering from gangrene are observed. In one case, a male patient with gangrene of his right toe complained of severe pain and sores upon untreated injury. Doctors applied leeches on the wounded toe to prevent amputation for 30 days. As a result of the treatment, the pain and blackness caused by gangrene in the finger area decreased. [35]

Chronic Non-Healing Wounds

One case describes a 73-year-old patient who complained of a persistent and non-healing large-scale ulcer in the lower leg area due to scratching after a mosquito bite. After the proper debridement of the wound and a total of five sessions of leech therapy once a week, the healthy granulation tissue started to emerge, and healing started gradually. The wound began to improve significantly, and proper epithelialization was achieved. Slowly the discharge was reduced and the wound healed completely. [36]

The 85-year-old patient had difficulty walking due to a large wound in the leg area, which caused pain and difficulty in walking. No matter what treatment was applied to the woman who had the chronic wound, it could not be healed and the patient whose leg was recommended to be amputated. The researchers applied bark paste of *Pongamia pinnata* along with medicinal leech therapy to achieve wound healing in this patient. At the end of the treatment protocol, all complaints of the patient were reduced and showed significant healing in the wounded area. [37]

In a case series evaluating the efficacy of leech therapy, four patients with varicose ulcers were included in this study. Medical leech therapy was applied to four patients of different ages, being affected by different diseases and who had ulcers on their legs. In this case series, out of four cases, three cases of the ulcers were completely healed and also showed remarkable improvement in other variables such as pain, discomfort on walking and itching. [38]

A 34-year-old female patient was suffering from a non-healing and necrotizing ulcer on her lower leg caused by systemic cutaneous sclerosis. The physicians applied a combination of leech therapy and Ayurvedic medicines to the patient's leg. After one month of treatment and three months of follow-up, the wound area got healed. [39]

Medical leech therapy, in addition to antiseptic drugs and unripe papaya dressing, was applied to a 60-year-old female patient who was at risk of below-knee amputation due to a diabetic foot ulcer. Successful healing was achieved due to increased vascularization and decreased congestion of the wound after leech therapy. At the end of the 3-month treatment period, necrotic areas disappeared, the patient could walk comfortably, and the wound was completely healed. Thus, the patient was discharged in good condition without losing any of her limbs. [40]

In diabetic foot ulcers that have become worse that may cause a limb amputation, some traditional treatments have been used along with medical leech therapy. Pain decreased immediately after leech therapy, and there was no wound on the toe after three weeks. Here, medical leech therapy had positive effects on wound healing. [41]

The case reports on leech therapy for the treatment of non-healing chronic wounds are given in Table 3, cases in which medicinal leech therapy was used.

Complications with Leech Therapy

Leech therapy has positive effects on people who are suitable for this treatment, and it is not possible to apply medicinal leech therapy to every individual (Table 4).

Different complications may be encountered in medical leech applications. The occurrence of infection after the leech application is a common situation with a rate of 2-36%. Bleeding, allergic reactions and bacterial infections are most common. Bacteria in the leech digestive tract can cause pneumonia, septicemia or gastroenteritis. It has been reported that the use of leeches without antibiotic treatment can cause bacterial infection at a rate of 20%. [42] Some studies show the infections caused by *Aeromonas hydrophila* because of the use of leeches in venous congestion of flaps and replantation. While some of these infections are acute and mild, infections that cause partial flap loss, have also been encountered. [43,44]

Bleeding is one of the most frequently reported complications. When the publications in the literature are examined, it has been reported that the bleeding due to leech therapy can be serious and excessive. In particular, Hirudin and histamine-like substances cause prolonged bleeding conditions. [45] A 25-year-old female patient who received leech therapy for varicose vein arrived in the emergency room 24 h after the leech

application because of the prolonged bleeding and received the necessary treatment. As the bleeding continued for 24 h, the physicians had to apply vein ligation under local anesthesia to the patient. [46]

Table 3. Cases in which medicinal leech therapy was used

The Cases of Traumatic Injuries					
Author(s)	**Year**	**Indication(s)**	**Number(s)**	**Treatment(s)**	**Efficacy**
Hullet et al. [27]	2007	Ear Laceration	n = 1	Ear Replantation + Medicinal Leech Therapy	Salvaged
Tachi et al. [29]	2018	Lip Amputation	n = 1	Lip Replantation + Medicinal Leech Therapy	Salvaged; venous drainage and revascularization
Jose et al. [31]	2013	Nose Laceration	n = 1	Nasal Flap + Medicinal Leech Therapy	The nasal flap remained viable without infection
TarazJamshid et al. [32]	2014	Finger Crush	n = 1	Finger Replantation + Medicinal Leech Therapy	The patient lost the fifth finger, but the third and fourth fingers salvaged
Frodel et al. [34]	2004	Traumatic Soft Tissue Avulsion	n = 4	Flaps + Medicinal Leech Therapy	Decreased venous congestion, increased healing
Lari et al. [35]	2021	Gangrene	n = 1	Medicinal Leech Therapy	The pain and blackness decreased
The Cases of Chronic Non-Healing Wounds					
Dhule et al. [36]	2022	The Cases of Chronic Non-Healing Wounds	n = 1	Medicinal Leech Therapy + Antiseptic Dressings	Proper epithelialization and complete wound healing was achieved
Balasooriya et al. [37]	2021	Ulcerated Wound	n = 1	Medicinal Leech Therapy + the Bark Paste of *Pongamia pinnata*	Healing was achieved: pain, itching, and smells were no longer present
Zarnigar, Md. [38]	2011	Ulcerated Wound	n = 4	Medicinal Leech Therapy	Three out of four cases healed completely
Sharma et al.	2020	Ulcerated Wound	n = 1	Medicinal Leech Therapy + Ayurvedic Medications	Achieved wound healing
Zaidi, S.A [40]	2016	Ulcerated Wound	n = 1	Medicinal Leech Therapy + Antiseptic Drugs & Unripe Papaya Dressing	Successful healing: increased vascularization and decreased congestion
Laila et al. [41]	2019	Diabetic foot Ulcer	n = 1	Medicinal Leech Therapy + Honey Curcumin Dressing	Decreased pain and increased wound healing

Table 4. Situations in which the application of medical leech therapy is not recommended[10]

Hematological Parameters	Patients receiving anticoagulant drug therapy	
	Patients with hemorrhagic disease, especially patients with hemophilia	
	Patients with severe anemia (Hb < 10)	
	Patients with an active bleeding focus	
Diseases	Patients with active tuberculosis or hypotension	
	Patients with advanced chronic disease:	Delayed wound healing
		Diabetes
		Arterial insufficiency
		The acute phase of mental illness.
Pregnant or Lactating Women	Since there is not enough data on the use of medical leeches in pregnant or lactating women, it should not be applied to these people.	
Immunological Parameters	Patients with acquired immune deficiency	
	Patients who are taking immunosuppressive therapy	
Others	Patients who will undergo surgical intervention	
Not recommended for children under the age of 18 years old		

Discussion

There are various review articles on the therapeutic effects, the effect mechanisms and indications of medical leech therapy and the content of medicinal leech saliva. [12,47,48] We have reviewed the studies in which medical leech therapy is used to promote wound healing, particularly in post-traumatic wounds and non-healing chronic wounds.

Because of the continuous bleeding caused by the anticoagulant substances in the leech saliva, the capillary network is relieved, and tissue congestion is greatly reduced. That also causes an increase in lymph flow, positive changes in local hemodynamics, ease of hemorheology, an increase in oxygen supply, improvement of tissue metabolism, and elimination of tissue ischemia. Thus, the survival rate of the affected area is increased.

Post-traumatic wounds and chronic non-healing wounds carry the risk of various complications. One of the most common complications is necrosis due to insufficient perfusion developing in the affected areas. Also, delayed or impaired wound healing can lead to limb amputation. For this reason, many methods have been sought in the scientific community to increase wound healing and perfusion rate.

The results of our literature review indicate that medicinal leech therapy has promising potential in the healing of post-traumatic and chronic non-healing wounds. Medical leech therapy, which has a history of thousands of years, is still the subject of many scientific studies today. Nevertheless, more studies are needed for the potential effects of medicinal leech therapy in wound healing should be clarified by further studies.

Conflict of Interest: The authors declare no conflict of interest.

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