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Message from the Editor-in-Chief

Dear colleagues,

As we leave behind the 102nd anniversary of the August 30 Victory of Turkey, the turning point of our struggle for independence; we wish for a world without wars and where human life reaches the value it deserves. In the words of our Great Leader Mustafa Kemal Atatürk, "Peace at home, peace in the world." is our motto. As medical people who have dedicated their lives to improving human health, we will maintain our struggle and our perspective open to innovations on this path. We will continue to share what we have learned from our studies to glorify human life and health.

We have prepared the third issue of Gulhane Medical Journal this year with this enthusiasm. We are happy to present you this issue, which includes remarkable studies and case reports in the field of medicine. We would like to express our endless thanks to all our editors who contributed to the preparation of this issue, our authors who shared their studies with our colleagues, and our valuable readers who showed interest.

Best regards

M. Ali Gülçelik, M.D., Prof.
Editor-in-Chief

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Medical interns' anxiety about their professional skills acquired during their internal medicine clerkship amid the COVID-19 pandemic

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Keywords: Medical education, clinical skills, clinical competence, anxiety, COVID-19 pandemic

ABSTRACT

Aims: The purpose of this study was to investigate the perceived anxiety status and related factors of Ege University Faculty of Medicine (EUFM) interns regarding the professional skills they acquired during their 4th year of Internal Medicine Clerkship (IMC) training during the Coronavirus disease-2019 pandemic.

Methods: This cross-sectional study was conducted between February and March 2022 with medical interns who received face-to-face (n=240) or online (n=120) IMC training at EUFM during the 2019-2020 academic year. The data were collected using a 38-item online survey questionnaire developed by a team of experts. Medical interns were asked to rate their anxiety status on a scale of 0-1 ("1" indicated anxiety "0" indicated no anxiety) for 22 diseases. The total score obtained from the list was labeled as the "medical interns' perceived anxiety total score" (minimum-maximum=0-22) which was also the primary outcome.

Results: Of the 90 study participants, 70.0% received face-to-face training during their internship in internal medicine. Demographic data revealed that 57.8% of participants were female, 20.0% expressed a desire to work abroad, and 52.2% reported feeling inadequacy in practicing their medical profession. Medical interns reported a mean perceived anxiety score of 13.1±5.0 out of 22 for managing various diseases. There was no significant difference in anxiety scores between the interns who received face-to-face (median=13.0) or online (median=14.0) training (p=0.482).

Conclusions: The study revealed that both online and face-to-face trained interns experienced similar levels of anxiety, with no significant difference in perceived anxiety scores between the two groups. Further research is required to assess the long-term effects of online education on the professional skills and anxiety of medical students, particularly in the context of its limitations in terms of practical skill acquisition.

Introduction

Anxiety is characterized by feelings of tension, worried thoughts, and physical changes like sweating, trembling, dizziness, rapid heartbeat, or increased blood pressure (1). The global prevalence of anxiety among medical students was recently estimated to be 33.8% in a meta-analysis of 69 studies involving 40,438 medical students. This prevalence is higher than that in the general population (2).

Although a reasonable amount of anxiety and stress can enhance student creativity and achievement, the strong

expectations and unrelenting demands of medical education can cause higher anxiety levels, impair student behavior, limit learning, damage personal relationships, and eventually impact patient care (3).

The Coronavirus disease-2019 (COVID-19) pandemic has significantly affected teaching and learning activities at all levels of education in Türkiye as well as worldwide (4,5). The main challenges reported were transferring most of the training and assessment activities to online platforms, reducing contact hours for learners and a lack of consultation with teachers when facing difficulties in learning and understanding (6).

The preclinical and clinical phases of medical education. Although both phases are important and essential, clinical teaching is central to medical education (7). This is because it not only takes place in real clinical environments, such as outpatient and inpatient clinics, but also provides opportunities to apply procedural, clinical, and communication skills in real-life scenarios. Additionally, it allows students to observe and learn professional skills from faculty members, doctors, nurses, and peers (8).

During the COVID-19 pandemic, the clinical training phase and all other training activities were severely disrupted worldwide and in Türkiye. Medical students have been isolated from clinical environments and patient interactions, preventing them from experiencing, practicing, and reinforcing their knowledge, skills, and attitudes in the clinical environment. This deprivation is an additional source of stress and anxiety for medical students (9,10).

At the Ege University Faculty of Medicine (EUFM), educational activities followed the declarations and decisions of the Turkish health authorities during the COVID-19 pandemic. The faculty administration collaborated effectively with faculty committees, commissions, and student representatives. According to these decisions, almost all preclinical and clinical training was conducted online, particularly during March-June 2020, the first four months of the pandemic. Theoretical lectures, integrated sessions, and panels were delivered synchronously online using Microsoft Teams. To enhance skills training, relevant departments and faculty members added videos, presentations, and text documents to the EUFM learning management system. It is planned to offer elective programs during the students' internship period to make up for the 4th and 5th-year clinical clerkship training that could not be completed between March and June 2020 (11).

It is inconceivable that online education could improve the clinical skills of medical students to an adequate level. During the COVID-19 pandemic, being away from the clinical environment and clerkship training might have increased medical students' anxiety regarding the acquisition and application of clinical skills. Although numerous studies have been conducted on the COVID-19 pandemic in Türkiye (4), few have investigated the pandemic's effects on medical education.

This study aimed to investigate the perceived anxiety levels and related factors among medical interns regarding the professional skills they acquired during their 4th year of Internal Medicine Clerkship (IMC) training during the COVID-19 pandemic.

Methods

Setting

This cross-sectional study was conducted with medical interns (6th year medical students) of EUFM who received their 4th year IMC training face-to-face or online in the 2019-2020 academic year at EUFM, which is the third public medical school established in Türkiye in 1955 and is currently carrying out a high standard six-year undergraduate curriculum for their students. The first three years of the program are the pre-clinical period, the next two years are the clerkships, and the last year is the internship period.

During the COVID-19 pandemic, two different groups of students received their IMC training, face-to-face and online. We aimed to reach the entire group of students who received IMC training either face-to-face (n=240) or online (n=120). Students who had received IMC training more than once or at another medical school were excluded. Ethical approval was obtained from the Ege University Faculty of Medicine Medical Research Ethics Board (decision no: 21-11.1T/5, date: 18.11.2021). The participation of medical interns was voluntary, and informed consent was obtained from all participants or, if participants were under 18, from a parent or legal guardian by approval on the landing page of the online survey.

Data collection tool

The data were collected using a 38-item survey questionnaire developed by a team of experts, including one public health specialist, one medical education faculty member, and three internal medicine specialists, based on relevant literature. Of the 38 items, 22 aimed to measure medical interns' perceptions of anxiety regarding their professional skills in certain diseases. This disease list was based on the EUFM IMC disease learning objectives list (12). The list was sent to nine internal medicine specialists who were asked to select diseases that could only be taught within the scope of an IMC.Diseases selected by seven or more specialists were included in the consensus list, resulting in 22 diseases. For each of these 22 diseases, the medical interns were asked to rate their anxiety status on a scale of 0-1, where "1" indicated anxiety and "0" indicated no anxiety. The total score obtained was labeled with the "medical interns' perceived anxiety total score" (minimum-maximum=0-22).

The remaining 16 items included in the survey questionnaire collected demographic data, including gender, age, career choice, healthcare professional in the family, economic level, place of residence, accommodation, internet availability, private room availability, technological tools used for online education during the pandemic, IMC training modality (face-to-face or online), extra course for National Medical Residency Entrance Exam in the past six months, student's first three years weighted grade point average (GPA) (GPA, out of 4.0), and the perception of professional competency.

The survey was conducted online using Google Forms and was sent to students via WhatsApp. The survey was available online for 45 days between February and March 2022, and two reminders were sent to the participants on the 2nd and 4th weeks after survey initiation. Participation was anonymous, and the authors had no access to the study data that could identify individual participants during or after data collection.

Statistical Analysis

The study data were analyzed using IBM Statistical Package for the Social Sciences statistics for Windows, version 25.0. Armonk, NY: IBM Corp. Categorical variables were presented as counts and percentages. Descriptive variables were presented as mean, standard deviation, quartile, or minimum and maximum values. A radar chart was used to record the medical interns' total perceived anxiety scores. Shapiro-Wilk test was used to evaluate whether the dataset was normally distributed. To compare medical interns' characteristics, the chi-square tests and independent samples t-test were used. Results showed that data were normally distributed. P values less than 0.05 were considered significant.

Results

Of the 360 medical interns who were invited to participate in the survey questionnaire, 90 responded, representing a response rate of 25.0%. Among the participants, 63 (70.0%) received their IMC training through face-to-face instruction, while 27 (30.0%) received it online. Of the respondents, 57.8% identified themselves as female, 40.0% as male, and 2.2% did not respond to the gender question. Of the medical interns, 20.0% expressed a desire to work abroad after graduation, and 74.4% indicated that they took extra courses to prepare for the National Medical Residency Entrance Exam within the past six months. Regarding their circumstances during the pandemic, 48.9% of the participants reported living in metropolitan areas, whereas 81.1% reported living with their families. In addition, 88.9% of participants reported having a private room during the COVID-19 pandemic, and 23.3% reported their family's economic status was good (Table 1).

Among the medical interns, 47 (52.2%) reported feeling incompetent in practicing the medical profession. Among those feeling inadequate, 66.7% received online and 46.0% received face-to-face IMC training. There was no statistically significant difference between these two groups regarding the perception of professional competency (p=0.073).

Regarding the participants' perception of anxiety toward their professional skills in managing various diseases, amyloidosis (n=83, 92.2%) was the most frequently cited disease in terms of eliciting anxiety among the students. This was followed by leukemia (n=81, 90.0%) and systemic vasculitis (n=76, 84.4%). In contrast, esophageal motility disorders, Cushing's disease, and megaloblastic anemia were the least frequently mentioned diseases, with 12 (13.3%), 14 (15.6%), and 30 (33.3%) participants indicating anxiety toward managing these conditions (Figure 1).

Table 1. Student characteristics

		Total (90)		Face-to-face (n=63)		Online (n=27)		
		n	%	n	%	n	%	p
Gender	Female	52	57.8	36	57.1	16	59.3	0.555
	Male	36	40.0	27	42.9	9.0	33.3	
	Not answered	2	2.2	0.0	0.0	2.0	7.4	
Career choice	Türkiye	71	78.9	51	82.3	20	74.1	0.377
	Abroad	18	20	11	17.7	7	25.9	
Taking extra courses for the National Medical Residency Entrance Exam in the past six months	No	23	25.6	16	25.4	7	25.9	0.958
	Yes	67	74.4	47	74.6	20	74.1	
Healthcare professionals in the family	No	60	66.7	42	66.7	18	66.7	1
	Yes	30	33.3	21	33.3	9	33.3	
Place of residence during the pandemic	Metropolitan	44	48.9	31	49.2	13	48.1	0.823
	City	24	26.7	18	28.6	6	22.2	
	District	20	22.2	13	20.6	7	25.9	
	Village	2	2.2	1	1.6	1	3.7	

Table 1. Continued

		Total (90)		Face-to-face (n=63)		Online (n=27)		
		n	%	n	%	n	%	p
Accommodation during the pandemic	With family	73	81.1	53	84.1	20	74.1	0.468
	With housemates	11	12.2	6	9.5	5	18.5	
	Alone	6	6.7	4	6.3	2	7.4	
Private room during the pandemic	No	10	11.1	7	11.1	3	11.1	1
	Yes	80	88.9	56	88.9	24	88.9	
Family economic level	Poor	5	5.6	1	1.6	4	14.8	0.142
	Fair	64	71.1	50	79.4	14	51.9	
	Good	21	23.3	12	19	9	33.3	
Internet connection problems during the pandemic	None	24	26.7	17	27	7	25.9	0.759
	Rarely	34	37.8	23	36.5	11	40.7	
	Sometimes	26	28.9	18	28.6	8	29.6	
	Frequently	6	6.7	5	7.9	1	3.7	
Tools used for online education	Computer	17	18.9	14	22.2	3	11.1	0.389
	Mobile devices	7	7.8	4	6.3	3	11.1	
	Both	66	73.3	45	71.4	21	77.8	
First three years weighted grade point average	60-70	23	25.6	16	25.4	7	25.9	0.597
	71-80	50	55.6	36	57.1	14	51.9	
	81-90	14	15.6	8	12.7	6	22.2	
	91-100	3	3.3	3	4.8	0	0	
Perception of professional competency	Inadequate	47	52.2	29	46	18	66.7	0.073
	Adequate	43	47.8	34	54	9	33.3	

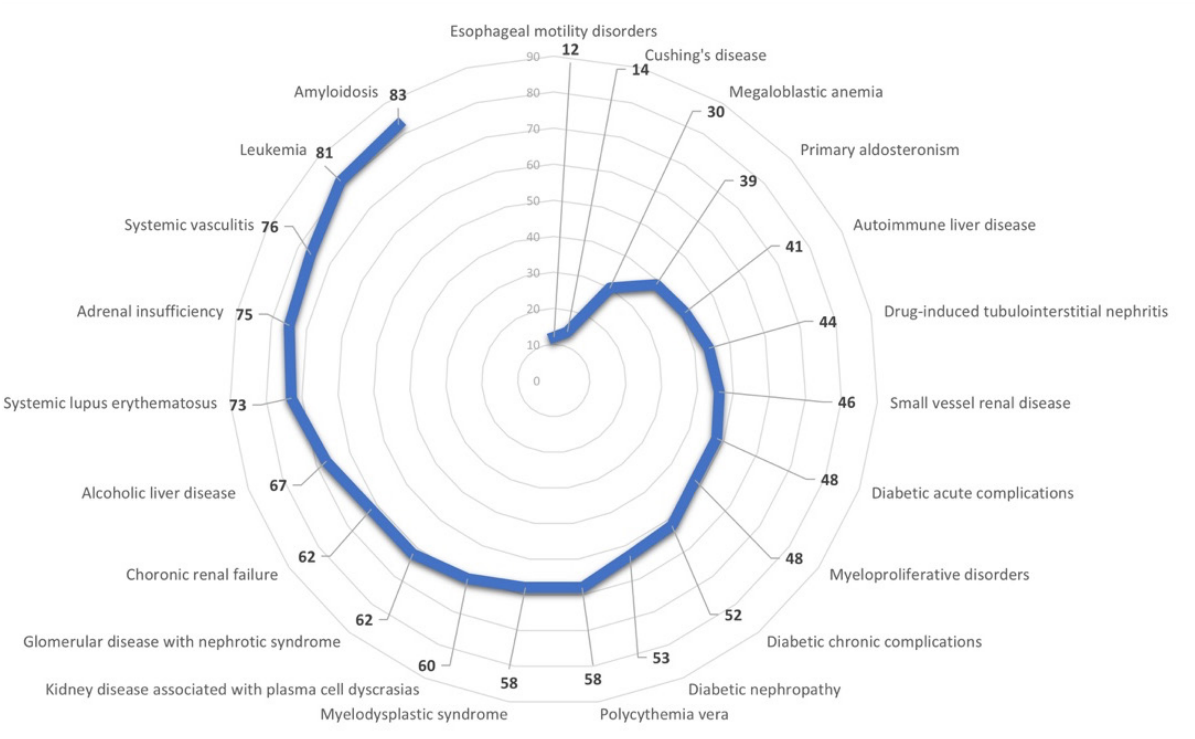


Figure 1. Medical interns' anxiety perceptions toward managing various diseases

Among the 22 diseases listed, medical interns' perceived mean total anxiety score was 13.1±5.0 [median 14.0, interquartile range (IQR)=7.2], 12.9±4.9 (median 13.0, IQR=7.0) in those who received face-to-face training and 13.7±5.4 (median 14.0, IQR=9.0) in those who received online training (p=0.482) (Figure 2).

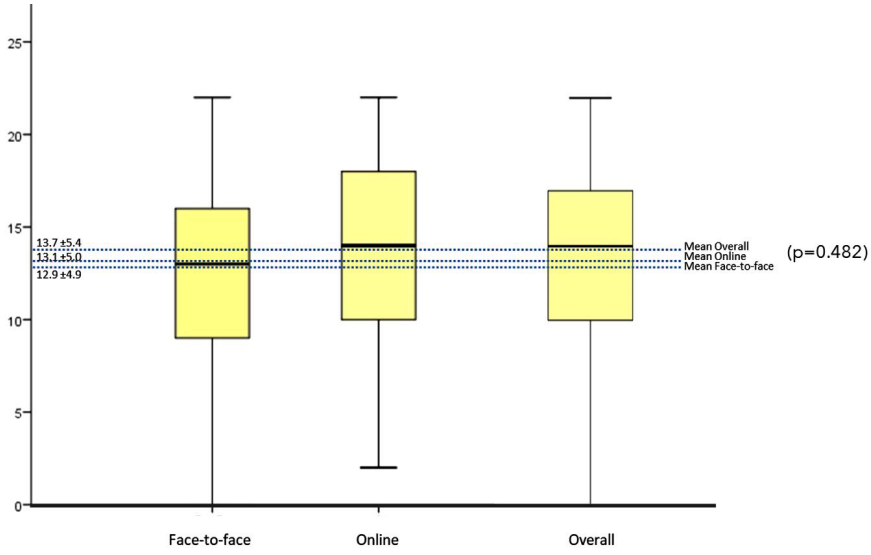
As shown in Table 2, the total mean perceived anxiety score was 5.1 points higher in the group that did not consider themselves competent than in the group that was confident (p<0.001). The total mean perceived anxiety score was 2.7 points higher in students who declared that they would continue their professional careers abroad (p=0.038). Additionally, although not statistically significant, students who reported a lower economic level had 2.5 points higher anxiety scores than those who reported higher levels of economic status (p=0.981). In the group of students with low academic achievement (GPA scores 60-70), the anxiety score was 2.1 points higher than those with a higher GPA, but the difference was not significant (p=0.561).

Discussion

We found a relationship between medical interns' perceptions of anxiety toward their professional skills in specific diseases learned during their 4th year of IMC training at EUFM and their feeling of inadequacy in practicing medicine, particularly during the COVID-19 pandemic. Although no statistically significant difference was observed, medical students who received online training reported feeling more inadequate when practicing medicine than those who received face-to-face training. This finding is consistent with a national survey study in which 46.7% of students reported that online training was "not good" for their practical courses (13).

In our study, the perceived anxiety levels of medical interns regarding professional skills in managing certain diseases were high, mirroring findings from a systematic review of 47 different international surveys of medical students concerning COVID-19 and mental health, which revealed increased rates of anxiety and depression worldwide during the pandemic (5).

A recent meta-analysis estimated an overall prevalence of 28% of anxiety in medical students during the COVID-19



				Percentiles		
	Median	Minimum	Maximum	25	50	75
Face-to-face	13	0	22	9	13	16
Online	14	2	22	10	14	18
Overall	14	0	22	9.75	14	17

Figure 2. Medical interns' anxiety levels in face-to-face and online education

Table 2. Factors associated with medical interns' perceived anxiety total scores

						95% CI		
Variable		**Mean 1**		**Mean 2**	**Mean difference**	**Lower**	**Upper**	**p**
Perception of professional competency	No	15.6	Yes	10.5	5.1	3.2	6.9	**<0.001**
Career choice	Abroad	15.2	Türkiye	12.5	2.7	0.2	5.3	**0.038**

CI: Confidence interval

pandemic (14). A nationwide study conducted in the United States reported that the anxiety levels of medical students increased more than three times during the pandemic period than during the pre-pandemic period (15). Correspondingly, the findings of our research are congruent with these observations, demonstrating similar trends in the escalation of anxiety levels. The COVID-19 pandemic resulted in the suspension of conventional face-to-face education worldwide, including in Türkiye. To address this need, EUFM swiftly implemented internet-based distance learning in alignment with global trends. This proactive measure was taken to ensure the continuity of education during the pandemic (11).

The present unforeseen shift has resulted in associated adjustment challenges. Specifically, a significant proportion (52.2%) of our participants reported a perceived inadequacy in their ability to apply their acquired knowledge and skills to professional practice after graduation. Two studies conducted during the COVID-19 pandemic revealed similar results, in which 53.3% (16) and 49% (17) of the interns expressed anxiety due to perceived professional inadequacy.

Our findings are consistent with a study conducted at Hacettepe University Faculty of Medicine with 103 last-year medical students (18). The authors reported that over half of the participants were unable to complete some of their clinical rotations due to the pandemic and expressed concerns about performing certain medical procedures with their current knowledge and skills upon graduation. Another study reported significantly higher levels of professional anxiety among intern physicians who did not feel competent as primary care physicians compared to those who did. In this group, 59% of the participants perceived themselves as insufficient in their roles as physicians, a perception that was correlated with a significantly higher level of professional anxiety, a finding that aligns with the outcomes of our research (19).

In our study, we observed a higher rate of self-reported feelings of inadequacy in practicing medicine among students enrolled in online education than those attending face-to-face training. Similarly, a survey administered to 370 medical students in the last year at Hacettepe University Faculty of Medicine in 2017 revealed that their perceived professional competency was significantly lower than expected (20). Furthermore, a statistically significant positive association was found between the feeling of professional competence and practical experience in medicine. During their last year of training, medical students were expected to enhance their competencies by applying their knowledge and skills to real clinical situations. However, they expressed dissatisfaction with the amount of active participation in medical practices during this period, which led to feelings of professional inadequacy (20).

The stress and anxiety experienced during pre-graduation education may impact patient care in future professional life (21,22). It has been reported that medical graduates nearing the end of their education express the greatest anxiety about professional practices related to their future professional careers (22).

One limitation of this study is its cross-sectional research design, which cannot capture changes in anxiety over time. In addition, no survey has been conducted before the COVID-19 pandemic to compare our results. Online surveys have become a crucial tool during the COVID-19 pandemic, allowing for the collection of real-time data despite the global restrictions implemented. Although the number of circulating surveys increased, response rates were lower during the pandemic era (23). The interns were reluctant to participate in our survey because they feared that the study's findings would lead to a mandatory clerkship to compensate for their lack of knowledge and skills. This also caused a small sample size in our study, which may limit the generalizability of the results.

Conclusion

Our investigation revealed a potential association between medical interns' anxiety regarding their professional skills in specific diseases learned during their 4th year of IMC training at EUFM during the COVID-19 pandemic and their self-reported inadequacy in practicing medicine. Notably, the study observed that interns trained online during the pandemic reported greater inadequacy feelings than interns trained face-to-face, highlighting the pandemic's substantial impact on medical education and student experiences. In light of our study and other related studies, the efficacy of online education during the pandemic on students' self-perceived professional competence and anxiety levels should be further evaluated, and more research should be conducted to identify necessary solutions.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Faculty of Medicine Medical Research Ethics Board (decision no: 21-11.1T/5, date: 18.11.2021).

Informed Consent: Informed consent was obtained from all participants or, if participants were under 18, from a parent or legal guardian by approval on the landing page of the online survey.

Authorship Contributions

Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: B.C., R.C., U.B., S.D., S.A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Outcomes and recurrence rates of four surgical techniques for treating vaginal vault prolapse

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ABSTRACT

Aims: This study aimed to compare the surgical outcomes of four distinct techniques for vaginal vault prolapse (VVP) after hysterectomy to identify the optimal approach.

Methods: This retrospective study was conducted using the data of patients who underwent VVP between 2010 and 2022 and had a history of hysterectomy. The surgical techniques evaluated were laparotomic sacrocolpopexy (LPSC), laparoscopic sacrocolpopexy (LSSC), sacrospinous ligamentopexy (SSLP), and laparoscopic lateral suspension (LLS). The study outcomes were the surgical duration, VVP recurrence, and adverse outcomes.

Results: The study included 77 women (age, mean±standard deviation: 58.96±9.96 years). LPSC, LSSC, SSLP, and LLS were detected in 27 (35%), 10 (13%), 31 (40.3%), and 9 (11.7%) cases, respectively. The duration of the surgery was significantly different among the groups (SSLP group: 115.96±51.29 min, LPSC group: 143.51±31.46 min, LLS group: 168.33±53.20 min, and LSSC group: 197.50±62.46 min, p=0.012). The recurrence rate of VVP was 11.11% in the LPSC group, 12.9% in the SSLP group, 11.11% in the LLS group, and 0.0% in the LSSC group (p=0.838). The rates of adverse outcomes in the early and late periods did not differ across the four groups, with p values of 0.274 and 0.556 (LPSC group: 18.52% and 18.52%, LSSC group: 20.0% and 20.0%, SSLP group: 6.46% and 22.58%, and LLS group: 0.0% and 22.22%).

Conclusions: Surgical techniques for VVP, including LPSC, LSSC, SSLP, and LLS, showed comparable outcomes and recurrence rates, except for the duration of surgery, which was the lowest in the SSLP group and longest in the LSSC group.

Introduction

Hysterectomy is one of the most common surgeries in gynecology (1). Pelvic organ prolapse (POP), such as vaginal vault prolapse (VVP), can be observed after hysterectomy (2) and causes serious morbidity in older women (2,3). Although post-hysterectomy VVP rates of 0.14% have been reported (3), this rate can rise to 11.6% in hysterectomy performed due to POP (4). The lifetime risk of surgery due to POP is 13% in the United States (5), and for many women, POP surgeries may lead

to voiding, defecation, and sexual dysfunction (5,6). However, surgery for VVP can improve the quality of life of patients (5,6).

Surgery for VVP, a subtype of POP surgery, is complex and requires experience (5,6). Various approaches for VVP surgery, including abdominal, vaginal, laparoscopic, and robotic, along with techniques such as sacrospinous fixation, colpocleisis, lateral suspension, and sacrocolpopexy, have been used to restore normal anatomy (7). Despite these efforts, ongoing studies and technological advancements continue to identify the optimal surgical technique for VVP. Four distinct techniques for VVP surgery, including laparotomic sacrocolpopexy (LPSC), laparoscopic sacrocolpopexy (LSSC), sacrospinous ligamentopexy (SSLP), and laparoscopic lateral suspension (LLS), are the preferred methods (5-8). Notably, a gap exists in the current literature, since no studies have compared the outcomes of these four techniques in VVP surgery. Hence, this retrospective study addressed this gap by comparing the surgical duration, recurrence rates, and adverse outcomes of four techniques.

Methods

Study population

This retrospective cross-sectional study evaluated women with symptomatic VVP who underwent surgery using four distinct techniques between 2010 and 2022. We collected data from the registry of the Urogynecology Clinic at the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Obstetrics and Gynecology Training and Research Hospital. The exclusion criteria were other surgical techniques for VVP, concomitant hysterectomy, recurrent VVP, missing data, and missing postoperative follow-up information. The Local Ethics Committee of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Obstetrics and Gynecology Training and Research Hospital approved the study protocol (date: 21.04.2022, number: 05/42).

Our clinic does not have a definite protocol regarding which technique will be used for each patient. Nonetheless, techniques such as SSLP and LPSC were previously preferred by surgeons, whereas with the development of technology, LSSC and LLS have been increasingly preferred by surgeons and patients. All surgeries in the current study were performed by surgeons at the Urogynecology Clinic of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Obstetrics and Gynecology Training and Research Hospital.

Data collection

Age, body mass index (BMI), obstetric and demographic characteristics, history of previous surgeries, evaluation of pelvic compartments using the Pelvic Organ Prolapse Quantification (POP-Q) system, duration of the surgery, intraoperative complications, preoperative and postoperative hemoglobulin values, postoperative early or late complications, length of hospital stay (LOS), postoperative follow-up time, and recurrence of cuff prolapse were collected using the patient files. POP-Q is performed according to the American College of Obstetricians and Gynecologists guidelines for all patients in our clinic guidelines (5) and is recorded in the patient's file. When the apex of the vagina was evaluated using the POP-Q system, cuff prolapses at stage 2 and above that occurred in the postoperative period were considered as recurrence (5,8). Due to the retrospective study design, recurrence rates were determined from the hospital's registration system using data entered after gynecological examinations.

The primary outcomes were differences in age, BMI, obstetric and demographic characteristics, stage of the POP-Q, duration of the surgery, and LOS among the four groups. The secondary outcomes were differences in the recurrence rates of VVP and adverse surgical outcomes (intraoperative complications, de novo pelvic pain, de novo urinary incontinence, and cystocele/rectocele) among the four groups.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (version 17; SPSS Inc., Chicago, IL, USA). Histograms, probability plots, and the Kolmogorov-Smirnov test were used to check the normal distribution. Normally distributed variables were expressed as mean±standard deviation (SD), skewed variables as median (interquartile range), and categorical variables as number and percentage. The chi-square test or Fisher's exact test was used to compare categorical variables across the four groups. Parametric variables were analyzed using one-way ANOVA, and non-parametric variables were analyzed using the Kruskal-Wallis test. The Bonferroni test was used for post-hoc analyses for variables significantly different across the groups. A $p<0.05$ was considered statistically significant.

Results

A total of 154 patients were evaluated, and 77 were included in the study (age, mean±SD: 58.96±9.96 years). LPSC, LSSC, SSLP, and LLS were detected in 27 (35%), 10 (13%), 31 (40.3%), and 9 (11.7%) patients, respectively. As shown in Table 1, a statistically significant difference was observed in the mean age and BMI of the four groups (p=0.003 and 0.011, respectively). Post hoc analysis revealed a significant difference in mean age between the SSLP (63.68±9.94 years) group and the LSSC (52.80±7.37 years) and LPSC (56.96±9.45 years) groups (p=0.011 and 0.044, respectively). However, the mean ages of the patients in the SSLP (63.68±9.94 years) and LLS (55.56±7.76 years) groups were similar in the post hoc analysis (p=0.140). The mean BMI was different only between the LSSC (25.13±2.69 kg/m^2) and the SSLP (30.68±4.44 kg/m^2) groups in

the post hoc analysis (p=0.009). The gravidity and parity were similar between all four groups (p>0.05), and all patients had a history of vaginal delivery (Table 1). The preoperative stages of POP-Q between the groups did not reach statistical significance (p>0.05) (Table 2).

Thirty-three (42.85%) cases of hysterectomy via the vaginal approach and 44 (57.15%) cases of hysterectomy via the abdominal approach were identified (Table 1), and there was no significant difference in the type of hysterectomy between the four groups (p>0.05). Additionally, the time from the previous hysterectomy was similar between the four groups (p=0.351). The duration of surgery was significantly different across the four groups (p=0.012); the shortest duration was identified in the SSLP group at 115.96±51.29 min, followed by LPSC at 143.51±31.46 min, LLS at 168.33±53.20 min, and LSSC at 197.50±62.46 min. There was a significant difference in the duration of surgery between the SSLP group and the LSSC and LLS groups (p<0.001 and 0.027, respectively); and no difference was noted between the SSLP and LPSC groups (p=0.178). Additionally, the duration of surgery was similar between the LPSC group and the SSLP and LLS groups (p=0.178 and 1.000, respectively); whereas there was a significant difference between the LPSC and LSSC groups (p=0.017). Intraoperative complications were observed in only one patient who underwent LSSC, as a bladder injury that was repaired laparoscopically in this patient.

The difference in LOS between the four groups did not reach statistical significance (p>0.05) (Table 1). However, the longest postoperative follow-up duration was observed in the LPSC group (78.19±50.23 months), whereas the shortest period was observed in the LLS group (36.56±7.81 months); the difference in the follow-up duration was significantly different only between these two groups (p=0.017). Adverse outcomes in the early and late postoperative stages did not differ between the four groups

Table 1. Demographic, obstetric, and surgical characteristics of the groups

	LPSC n=27	LSSC n=10	SSLP n=31	LLS n=9	p value
Age, years, mean±SD	56.96±9.45	52.80±7.37	63.68±9.94	55.56±7.76	**0.003**[a]
Gravidity, n, mean±SD	3.95±1.98	3.40±0.96	4.74±2.12	4.00±1.58	0.205[a]
Parity, n, mean±SD	3.10±1.33	2.50±0.70	3.74±1.67	3.11±1.61	0.108[a]
BMI, kg/m^2, mean±SD	28.24±3.75	25.13±2.69	30.68±4.44	29.67±8.30	**0.011**[a]
Time since the previous hysterectomy, years, mean±SD	10.92±6.76	7.88±7.64	11.46±7.94	7.00±6.25	0.351[a]
Type of previous hysterectomy, % (n)					
Abdominal approaches, 57.14 (44)	40.7 (11)	40.0 (4)	41.9 (13)	55.6 (5)	0.884[b]
Vaginal approaches, 42.86 (33)	59.3 (16)	60.0 (6)	58.1 (18)	44.4 (4)	
Preoperative Hb, g/dL, mean±SD,	13.23±1.27	13.71±1.05	13.01±1.04	13.08±1.16	0.432[a]
Postoperative Hb, g/dL, mean±SD,	11.12±1.21	11.34±1.08	10.69±1.95	11.09±0.62	0.392[a]
Delta Hb, g/dL, mean±SD	1.91±0.76	2.35±1.86	2.37±0.87	1.99±0.84	0.592[a]
Duration of surgery, minutes, mean±SD	143.51±31.46	197.50±62.46	115.96±51.29	168.33±53.20	**0.012**[a]
Length of hospital stay, days, mean±SD	3.01±2.04	3.30±3.09	2.45±0.88	2.11±0.33	0.307[a]
Postoperative follow-up period, months, mean±SD	78.19±50.23	56.06±18.40	56.70±38.22	36.56±7.81	**0.012**[a]

The results are significant at p<0.05, [a]: One-way ANOVA test, [b]: Fisher's exact test.
BMI: Body mass index, n: Number, Hb: Haemoglobin, LLS: Laparoscopic lateral suspension, LPSC: Laparotomic sacrocolpopexy, LSSC: Laparoscopic sacrocolpopexy, SSLP: Sacrospinous ligamentopexy, SD: Standard deviation

Table 2. Evaluation of pelvic compartments across the groups with quantification of the Pelvic Organ Prolapse Quantification system

	LPSC n=27	LSSC n=10	SSLP n=31	LLS n=9	p value
Apical compartment, stage, median (IQR)	4 (1)	4 (1)	4 (1)	3 (1)	0.603
Anterior compartment, stage, median (IQR)	1 (3)	2 (4)	0 (4)	3 (3)	0.659
Posterior compartment, stage, median (IQR)	0 (1)	0 (0)	0 (2)	0 (2)	0.155

The results are significant at the level of 0.05. Kruskal-Wallis H test.
IQR: Interquartile range, LLS: Laparoscopic lateral suspension, LPSC: Laparotomic sacrocolpopexy, LSSC: Laparoscopic sacrocolpopexy, n: Number, SSLP: sacrospinous ligamentopexy

(p=0.274 and 0.974, respectively) (Table 3). Considering the early postoperative findings, surgical site infection (n=3 LPSC group; n=1 SSLP group), fever of unknown origin (n=2 each in the LPSC and SSLP groups), nephrostomy due to ureteral injury (n=1 LSSC group), postoperative pulmonary dysfunction (n=1 LSSC group), and postoperative acute coronary syndrome (n=1 LPSC group) were identified.

Late postoperative findings included urinary incontinence, cystocele/rectocele, pelvic pain, and VVP recurrence. Recurrent VVP was detected in 8 (10.38%) cases in all patients, of whom 3 (37.5%) belonged to the LPSC group, 4 (50.0%) to the SSLP group, and 1 (12.5%) to the LLS group. No recurrence of VVP was observed in the LSSC group (Table 3). The difference in recurrence rates between the groups was non-significance (p=0.838). Six percent of the patients had de novo urinary incontinence (urge and stress), 6.5% had cystocele/rectocele, 1.3% had pelvic pain, and 10.4% had recurrent VVP. The difference in the incidence of late postoperative outcomes across the four groups did not reach statistical significance (p>0.05) (Table 3). Mesh erosion, sexual dysfunction, and new dyspareunia were not observed in any of the patients.

Discussion

Conservative treatment modalities, such as pelvic floor physiotherapy and pessaries, are available as first-line treatment for POP; however, reconstructive or obliterative surgeries for VVP are planned when conservative treatments fail or the prolapse is severe (5). In the current study, the outcomes of four surgical techniques for VVP were evaluated retrospectively. Overall, the four surgical techniques had similar surgical outcomes, with the only difference being the duration of the surgery.

Various techniques are used for VVP surgery; nonetheless, newer approaches are being developed using contemporary technology. Sacrocolpopexy is the gold standard treatment for VVP (9). It was reported to be superior to SSLP; however, the duration of the surgery and recovery time are longer than those of SSLP (10). Similarly, SSLP was found to be the shortest and easiest technique in our study. Nonetheless, LOS and postoperative outcomes were similar between the four groups examined in our analysis. In a meta-analysis evaluating POP surgery, vaginal suture suspension to various pelvic ligaments was found to be inferior when evaluated as outcomes of apical failure from abdominal sacrocolpopexy (any route) with synthetic mesh; however, anterior and posterior failures, awareness of recurrence, reoperation, intraoperative bladder and ureter injuries, and postoperative lower urinary tract symptoms were similar in both surgery types (11). The only case in our study cohort who underwent bladder injury and nephrostomy due to ureteral injury belonged to the LSSC group; no urinary tract injury was observed in any of the other cases. Long-term surgical outcomes were similar between the sacrocolpopexy (laparotomic and laparoscopic) and SSLP groups in the current study.

Table 3. Postoperative adverse outcomes across four groups

	Total cases n=77	LPSC n=27	LSSC n=10	SSLP n=31	LLS n=9	p value
Early postoperative outcomes, n (%)						
No	68 (88.31)	22 (81.48)	8 (80.0)	29 (93.54)	9 (100)	0.274
Yes	9 (11.69)	5 (18.52)	2 (20.0)	2 (6.46)	0 (0.0)	
Type of early postoperative outcomes, n (%)						
Surgical site infection	4 (5.19)	3 (11.11)	0 (0.0)	1 (3.22)	0 (0.0)	0.272
Fever of unknown origin	2 (2.59)	1 (3.70)	0 (0.0)	1 (3.22)	0 (0.0)	
Nephrostomy due to ureteral injury	1 (1.29)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	
Postoperative pulmonary dysfunction	1 (1.29)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	
Postoperative acute coronary syndrome	1 (1.29)	1 (3.70)	0 (0.0)	0 (0.0)	0 (0.0)	
Late postoperative outcomes, n (%)						
No	61 (79.22)	22 (81.48)	8 (80.0)	24 (77.41)	2 (22.22)	0.566
Yes	16 (20.08)	5 (18.52)	2 (20.0)	7 (22.58)	2 (22.22)	
Types of late postoperative outcomes, n (%)						
De novo urinary incontinence	2 (2.59)	1 (3.70)	0 (0.0)	1 (3.22)	0 (0.0)	0.443
De novo cystocele/rectocele	5 (6.49)	0 (0.0)	2 (20.0)	2 (6.46)	1 (11.11)	
De novo pelvic pain	1 (1.29)	1 (3.70)	0 (0.0)	0 (0.0)	0 (0.0)	
Recurrence of vaginal vault prolapse	8 (10.38)	3 (11.11)	0 (0.0)	4 (12.90)	1 (11.11)	

The results are significant at p<0.05.
LLS: Laparoscopic lateral suspension, LPSC: Laparotomic sacrocolpopexy, LSSC: Laparoscopic sacrocolpopexy, n: Number, SSLP: Sacrospinous ligamentopexy

Minimally invasive approaches, such as laparoscopic or robotic approaches, are preferred to LPSC surgery when a trained surgical team and appropriate equipment are available, and similar outcomes have been reported after POP surgery in both the short and medium-term (10-12). No difference has been reported between laparotomic and laparoscopic approaches for sacrocolpopexy in the context of its therapeutic effect on apical vaginal prolapse and incidence of recurrence has been reported (11-13). However, LSSC is considered superior to LPSC in terms of the quantity of blood loss, LOS, and risk of ileus (12,13). In our study, although the LOS was similar between patients who underwent LSSC and LPSC, surgical site infection, de novo urinary incontinence, pelvic pain, and VVP recurrence were predominant in the LPSC group, whereas urinary tract injury and *de novo* cyctorectocele were observed in the LSSC group. Recurrence of cystocele and mesh-related complications were reported to occur more frequently in the LSSC group than in the LPSC group (14).

Although sacrocolpopexy is the preferred laparoscopic technique for the treatment of POP, its duration is longer and the learning curve is steep (15). In the current study, the parameter that differed most between the groups was the surgery duration. The first randomized controlled trial on a comparison of LSSC and SSLP was designed in 2017; the long-term (5-year) outcomes of this study will reveal the advantages and disadvantages of sacrocolpopexies performed with minimally invasive approaches over ligament fixation (16). McFerrin et al. (17) and Costantini et al. (18) showed that the transition from open to robotic surgery was feasible for POP without compromising improvements in pelvic anatomy, urinary incontinence, and injury to the lower urinary tract.

New techniques with minimally invasive approaches are required to shorten the surgery duration (19). In the LLS technique, which was first described by Dubuisson and Chapron (1998) (20) for POP, presacral injuries were rare because there were no surgical dissections in the presacral region. In the current study, LLS was a minimally invasive approach that resulted in a shorter surgery duration than LSSC, while late postoperative outcomes were similar. Chatziioannidou et al. (21) reported that the rate of repeat surgery using the LLS technique was 5.1%, and the recovery rate was 87.3%. Dubuisson and Chapron (20) reported a success rate of 86% and a recurrence rate of 4.6% using the LLS technique with a shorter follow-up time of 18 months. Mereu et al. (22) reported that 6.4% of female patients undergoing the LLS series underwent repeat surgery for POP at a 2-year follow-up. However, these studies included a small number of patients who underwent hysterectomy (19-21), and the incidence of intraoperative complications, such as urinary tract, presacral, and lower gastrointestinal tract injuries, was also lower. In the current study, no intraoperative complications were detected, and only one case each had *de novo* cystocele/rectocele and recurrence of VVP. LLS surgery, an effective procedure to treat anterior and apical POP, has been related to a lower risk of mesh-related complications, and, therefore, widely preferred for VVP surgery by reducing other potential complications (19-21). However, further randomized controlled studies are needed to validate these findings.

In the current study, the number of patients recruited was small due to the strict exclusion criteria, the low number of patients who underwent postoperative follow-up and therefore could be included in the calculation of recurrence rates, and the generally infrequent incidence of VVP surgery. Due to the retrospective study design, the number of patients who underwent laparoscopic techniques, such as LSSC and LLS, was small. On the other hand, all of the cases had a history of hysterectomy and similar POP-Q stages, which can be considered a major strength of the study. Despite these shortcomings, to the best of our knowledge, this has been the first study to compare four surgical techniques (LPSC, LSSC, LLS, and SSLP) for VVP. In addition, this study may draw the attention of clinicians towards minimally invasive techniques for VVP surgery, and encourage randomized controlled studies on this subject.

Conclusion

The optimal surgical technique for VVP continues to be a challenge, as VVP surgeries are difficult, protracted, and require surgical skills. Although SSLP and LPSC are no longer preferred when other minimally invasive surgeries are feasible, they had similar surgical outcomes to the other techniques in the current study. LLS is a reliable technique that can shorten the surgical duration of LSSC. The current study found that the four techniques for VVP had similar surgical outcomes and recurrence rates, with the only difference in the duration of surgery (SSLP < LPSC < LLS < LSSC). However, considerable developments have been observed in VVP surgery in recent years due to improvements in technological and surgical skills. Further studies are necessary to evaluate factors that can improve the safety and reliability of VVP surgery.

Ethics

Ethics Committee Approval: This cross-sectional, retrospective study was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Obstetrics and Gynecology Training and Research Hospital, Ankara, Türkiye (approval no: 05/42, date: 21.04.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.A., B.Ş., A.K.Ö., T.K.T., V.K., Concept: A.A., V.K., Y.E.Ü., Design: A.A., V.K., Y.E.Ü., Data Collection or Processing: A.A., B.Ş., A.K.Ö., T.K.T., Analysis or

Interpretation: A.A., Y.E.Ü., Literature Search: A.A., B.Ş., A.K.Ö., T.K.T., Y.E.Ü., Writing: A.A., B.Ş., A.K.Ö., T.K.T., V.K., Y.E.Ü.

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Effects of cold application before subcutaneous injection of low-molecular-weight heparin on pain, bruising, and hematoma formation: A randomized controlled trial

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ABSTRACT

Aims: With daily subcutaneous low-molecular-weight heparin (LMWH) injections for long periods, there is a high risk of local side effects, such as pain, bruising, and hematoma. This study aimed to compare the impact of cold application on post-injection pain, bruising, and hematoma in patients receiving subcutaneous LMWH following urologic surgery.

Methods: This was a single-blind, randomized control trial. Urology inpatients were randomly assigned to three groups; Group 1: cold application for 2 min before injection, Group 2: cold application for 5 min before injection, and Group 3: control group with no cold application. Post-injection pain was assessed immediately after injection. Bruising and hematoma were assessed at 48th and 72nd hours.

Results: The study included 26 patients in Group 1 (age=63.85±9.89 years; male=84.6%), 26 patients in Group 2 (age=64.54±11.66 years; male=80.8%), and 26 patients in Group 3 (age=65.65±11.36 years; male=88.5%). The pain scores in Groups 1 (11.58±12.06) and Group 2 (6.08±9.11) were lower than Group 3 (28.35±20.97) ($p<0.001$). At the 48th hour, the frequency of bruising in Group 1 (11.5%) and Group 2 (11.5%) was lower than that in Group 3 (38.5%) ($p=0.021$), and the bruise size in Group 1 (4.00±1.73 mm) was lower than that in Group 3 (15.00±7.07 mm) ($p=0.020$). No hematomas was detected in any patient groups at the 48th and 72nd hours.

Conclusions: This study showed that although cold application for 2 or 5 minutes before injection reduced pain and bruising frequency, application for 2 minutes was more effective on bruise size.

Introduction

Side effects, such as pain, bruising, and hematoma, frequently occur following subcutaneous (SC) injection (1). Adverse effects not only result in physical and psychological consequences leading to their reluctance toward subsequent injections but also pose challenges for nurses when selecting injection sites for repeated administrations because of induration and hematoma at the injection site (2-6). Side effects after SC injection are a significant issue, particularly for patients undergoing prolonged anticoagulant therapy (1,6-8).

In the literature, there are various modalities to prevent pain, bruising, and hematoma at the injection site following SC injection, including compression or massage after the injection, application of dry cold or heat, aspiration of the syringe before injection, and slow injection (2,4,5). Among them, cold application is a preventive measure to minimize the effect of SC heparin injections. Moist cold application, dry ice pack, cold gel pack, or vapor cooling spray can be used (9-11). Slowing blood circulation within the targeted tissue cold application exerts several beneficial effects, including curtailing edema and inflammatory responses,

diminishing pain stemming from swelling, regulating bleeding by constraining the capillary surface, inducing local anesthesia by decreasing pain sensitivity, and enhancing coagulation by elevating blood viscosity (1,5,9,11-13).

Some studies indicated no significant effect of cold application on the size and frequency of bruising and hematoma (8,14), whereas others showed benefits (9,12,13,15-20). Despite the lack of effect on bruising and hematoma following cold application, patients' pain perception may has been shown to improve significantly (1,8).

Although many studies have been conducted, most did not report firm conclusions, indicating the need for further studies (5,9,12,20). Particularly, the effectiveness of cold application in reducing pain, bruising, and hematoma following low-molecular-weight heparin (LMWH) therapy and the optimal duration of cold application need to be clarified. Hence, the current study aimed to assess the impact of cold application at varying durations on the incidence of pain, bruising, and hematoma in patients receiving SC LMWH.

Methods

Study design and participants

This single-blind randomized controlled study was conducted from January 2017 to June 2017 on patients who underwent SC LMWH following urologic surgery.

Patients admitted to the urology clinic of a training and research hospital who received postoperative SC heparin treatment were included. The inclusion criteria were age 18 years or older, daily LMWH treatment through a pre-filled syringe containing 40 mg of enoxaparin sodium in 0.4 mL, no visual or auditory impairments, no known coagulation disorders, normal platelets, partial thromboplastin time, and international normalized ratio (INR) values, no hematologic disorder or injury on the abdominal wall, no injections other than enoxaparin sodium at the abdominal site during the study, and willingness to participate in the study. The patients were excluded if they were pregnant, had bleeding at the injection site, experienced pre-existing pain at any body site before injection, presented with conditions such as incisions, drains, scar tissue, lipodystrophy, or infection symptoms at the abdominal site that hindered injection application or were not inclined to participate in the study. This study was registered in the ClinicalTrials.gov Protocol Registration and Results System under the identifier: NCT05771285.

Sample size calculations and power analyses were performed considering the values for bruising reported in a previous study (17). As a reference, it was expected that the bruising area would measure 10.2±5.9 mm in the group without cold application and 6.5±3.1 mm in the group with cold application. Taking a type 1 error of 5% and a type 2 error of 20%, a total of 78 patients were required, comprising 26 patients in the 2-min cold application group, 26 patients in the 5-min cold application group, and 26 patients in the control group. The CONSORT diagram is presented in Figure 1.

The evaluation of bruising and hematoma at the 48th and 72nd-hour post-injection was performed by the same nurse who was blinded to participant grouping.

Randomization

The participants were randomized based on age and gender (14,21,22) using block randomization by stratifying gender blocks into three age groups (www.random.org).

Fifty-five individuals were excluded from the study due to infection, scar tissue, inflammation, incision, or drain at the intended injection site. The remaining patients were categorized into three groups. Group 1 and Group 2 underwent a 2-minute and 5-minute cold application, respectively, at the injection site before injection. Group 3 underwent standardized injection without cold application (Figure 1).

Standard SC injection technique

SC injection was performed by the same researcher following a standardized technique.

- One side of the abdomen was selected 5 cm from the umbilicus.

- After hands were washed, the procedure was explained to the patient, the patient was placed in a semi-fowler position during the injection, the injection site was cleaned with 70% alcohol in circular motions softly outward from the center, and the injection site was left to dry before the injection.

- After drying the area, the skin and SC tissue at the injection site were pinched between the thumb and index finger.

- We used a 25-gauge prefilled LMWH (enoxaparin sodium) syringe with a 1.26 cm needle length and an airlock.

- The needle was inserted into the tissue at a 90° angle, and no aspiration was applied for blood control.

- The injection time of the medication was 10 seconds. Then the needle was withdrawn at the same angle.

- The tissue was pinched between two fingers throughout the injection period and was freed after the needle was withdrawn.

- After the injection process was completed and the needle was withdrawn, dry cotton was pressurized on the injection area. The whitening of the nail edge of the finger exerting pressure was used as the standard of the exerted pressure.

- After exerting pressure with dry cotton, the patient was asked to indicate the severity of the pain felt on the visual analog scale (VAS).

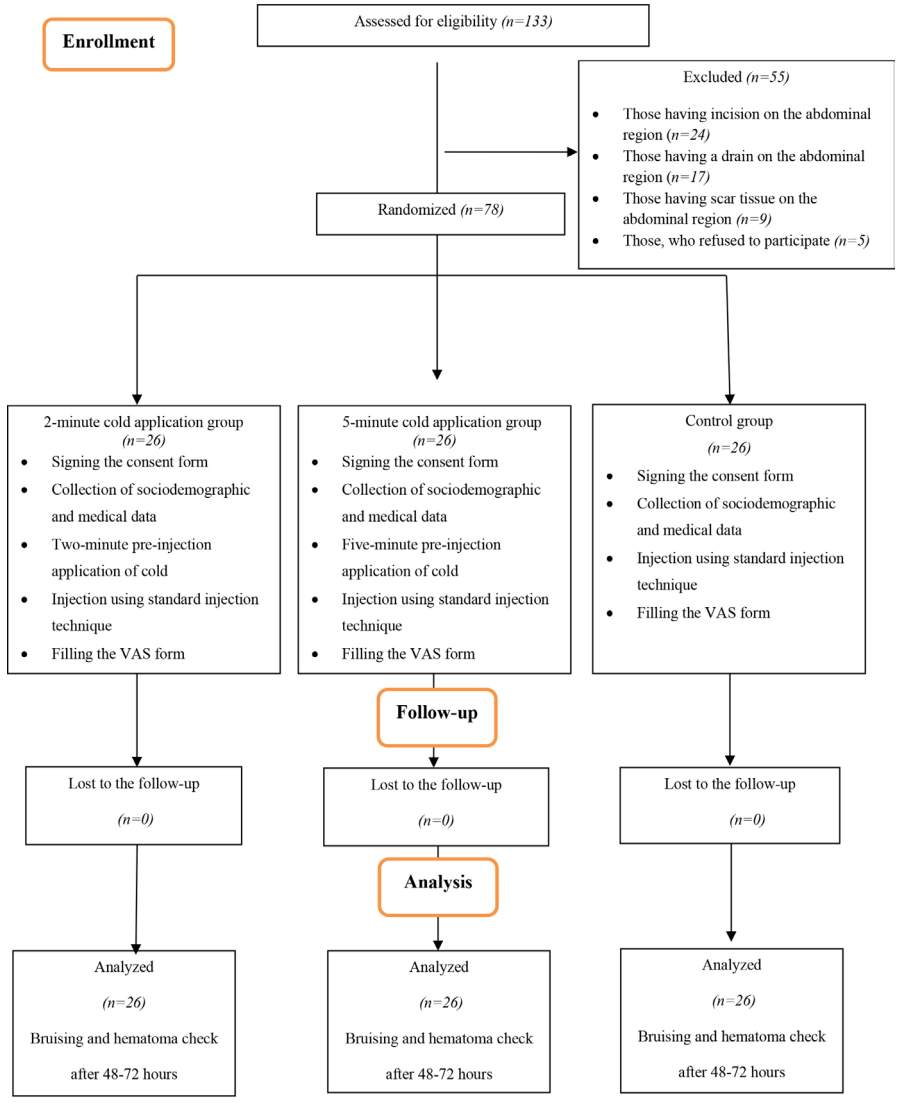

Figure 1. The flow diagram of the study

- After injection, the area was marked with an acetate pen by drawing a circle.

- The patient was informed not to scratch or rub the injection area. No other SC injection or application was made in the area until the assessment of bruising and hematoma at the injection site.

- Other injection areas were chosen when another heparin treatment was needed.

Data collection

We collected sociodemographic and clinical data using a standardized form developed based on relevant literature (1,7,14,16,17,19,23-26). Descriptive characteristics included age, gender, marital status, employment status, and educational background. Prior injection experience, fear of injection, and previous surgical operations were recorded. Body mass index, waist circumference, and prothrombin time with the INR were recorded before the intervention.

A follow-up form was created to systematically document the time and date of injection and monitor pain, bruising, and hematoma at the 48th and 72nd-hours post-injection by the same researcher blinded to the protocol.

We assessed pain and severity using a VAS (VAS, 0-100 mm) (27-29). Immediately after SC injection, patients were asked to mark the severity of pain on a VAS.

A transparent measurement tool, an acetate pen, and millimetric measurement paper were used to measure the bruising size. Adapted from a previous study (18), bruise severity was defined as “bruise present” if color changes were 2 mm or larger, and “no bruise” if color changes were less than 2 mm. At the 48th and 72nd hours after the injection, the injection site was evaluated visually and by palpation for hematoma. A pilot

test was carried out with 5 patients to determine the functionality of the forms. Patients involved in the pilot study were excluded from subsequent assessments.

Outcomes

The outcome measures were between-group differences in VAS score immediately after injection, bruising frequency and size at the 48th and 72nd hours, and hematoma frequency and size at the 48th and 72nd hours.

This study was approved by the Clinical Research Ethics Committee of the Keçiören Training and Research Hospital (decision no: 2012-KAEK-15/1257, date: 11.01.2017).

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to check the normal distribution. Normally distributed variables were expressed as mean±standard deviation, skewed variables as median (minimum-maximum), and categorical variables as number and percentage. Multiple comparisons were performed using the Kruskal-Wallis or ANOVA test for continuous variables and the chi-square test for ratio variables. The significance level was set at $p<0.05$.

Results

The study included 26 patients in Group 1 [age=63.85±9.89 years; male=84.6%], 26 patients in Group 2 [age=64.54±11.66 years; male=80.8%], and 26 patients in Group 3 [age=65.65±11.36 years; male=88.5%] (Table 1). No statistically significant differences were observed among the groups in sociodemographic and clinical characteristics.

Table 1. Sociodemographic and clinical characteristics of the patients in groups (n=78)

Variables	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	Test statistics	p
Age (years) (mean±SD)	63.85±9.89	64.54±11.66	65.65±11.36	0.179*	0.837
Gender, n (%)					
Female	4 (15.4)	5 (19.2)	3 (11.5)	0.591**	0.744
Male	22 (84.6)	21 (80.8)	23 (88.5)		
Marital status, n (%)					
Married	26 (100.0)	23 (88.5)	22 (84.6)	4.080**	0.130
Single	-	3 (11.5)	4 (15.4)		
Educational background, n (%)					
Primary school	17 (65.4)	19 (73.1)	16 (61.5)	2.885**	0.577
High school	3 (11.5)	5 (19.2)	5 (19.2)		
≥University	6 (23.1)	2 (7.7)	5 (19.2)		
Working status, n (%)					
Employed	5 (19.2)	3 (11.5)	4 (15.4)	0.591**	0.744
Unemployed/retired	21 (80.8)	23 (88.5)	22 (84.6)		
Cohabitation, n (%)					
Living alone	-	2 (7.7)	5 (19.2)	7.084**	0.132
Married/not living with his/her children	10 (38.5)	12 (46.2)	11 (42.3)		
Living with a partner and children	16 (61.5)	12 (46.2)	10 (38.5)		
Operations, n (%)					
Prostate surgery	14 (53.8)	16 (61.5)	11 (42.5)	Not assessed	
Kidney surgery	9 (34.6)	-	9 (34.5)		
Bladder surgery	1 (3.8)	10 (38.5)	3 (11.5)		
Testicle surgery	2 (7.7)	-	1 (3.8)		
Other urological surgeries	-	-	2 (7.7)		
BMI (kg/m^2) (mean±SD)	29.69±4.86	28.69±5.09	35.38±30.78	1.021*	0.365
Navel circle (cm) (mean±SD)	105.27±16.04	108.12±14.25	107.69±12.73	0.296*	0.745
Subcutaneous injection experience in the abdominal region, n (%)	6 (23.1)	3 (11.5)	7 (26.9)	2.044**	0.360
Fear of injection, n (%)	8 (30.8)	9 (34.6)	12 (46.2)	1.427**	0.490
PT (mean±SD)	14.50±1.11	14.35±0.79	15.40±2.97	2.355***	0.308
INR value (mean±SD)	1.04±0.14	1.02±0.08	1.11±0.28	1.564***	0.457

Data is represented either as the mean±SD or as the frequency.
*One-way ANOVA, **Chi-square, ***Kruskal-Wallis test was used in comparisons.
SD: Standard deviation, BMI: Body mass index, PT: Prothrombin time, INR: International normalized ratio

Table 2 presents the comparisons of VAS pain scores among the groups. VAS pain scores in Group 1 (11.58±12.06) and Group 2 (6.08±9.11) were significantly lower than those in Group 3 (28.35±20.97) (p<0.001 for both).

Table 3 shows the frequency of bruising among groups at the 48th and 72nd hours following heparin injection. At 48 hours, the frequency of bruising in Group 1 (11.5%) and Group 2 (11.5%) were significantly lower than Group 3 (38.5%) (p=0.021). At 72 hours, there was no significant difference in bruising frequency among the three groups (p>0.05).

Table 4 shows bruise size at 48 and 72 hours. At 48 hours, the bruise size in Group 1 (4.00±1.73 mm) was significantly lower than that in Group 3 (15.00±7.07 mm) (p=0.020). At 72 hours, bruise size was similar between the groups (p>0.05).

We observed no hematomas in any group at the 48 and 72 hours.

Discussion

This study showed that although cold application for 2 or 5 min before injection reduced pain and bruising frequency, a 2-min cold application was superior to a 5-min cold application for reducing bruise size. In addition, no hematoma was detected in the intervention or control groups at the 48th and 72nd hours. SC LMWH injection is commonly performed in nursing practice. Therefore, the results of this study may help guide routine practice to reduce pain and bruising after SC injections. Additionally, we observed no differences among the groups concerning individual factors or medications that could contribute to pain, bruising, and hematoma development following SC injections. In addition, we applied a standardized injection technique to all patients, which can also help decrease the effect of confounding factors and directly reveal the impact of cold application.

Some studies have shown that cold application increases pain tolerance (30-33). Cold exposure decreases catecholamine levels, increases endorphin levels, and delays the transmission of pain signals to the central nervous system, contributing to reduced pain intensity. Pain receptors, which are free nerve endings, are located in the outer layers of the skin. Therefore, acute pain occurs when the needle is inserted into the skin. Cold application interrupts pain perception by affecting sensory nociceptors. It also reduces transmission time and synaptic activities in peripheral nerves. When nerve temperatures decrease, sensory and motor transmission speeds decrease, subsequently preventing the perception of pain is realized

Table 2. VAS pain scores among the groups

	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	χ^2	p
VAS pain score (0-100, mm), mean±SD, median (min-max)	11.58±12.06, 10.00 (0-40)	6.08±9.11, 0.00 (0-25)	28.35±20.97, 20.00 (0-70)	21.661	**<0.001**[a,b]

χ^2: Kruskal-Wallis test. [a]: Comparison between 2-minute cold application group and control group, [b]: Comparison between 5-minute cold application group and control group.
VAS: Visual analog scale, SD: Standard deviation, min-max: Minimum-maximum

Table 3. The frequency of bruising at 48th and 72nd hours by groups (n=78)

The frequency of bruising	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	χ^2	p
48th hour					
No bruise (<2 mm), n (%)	23 (88.5)	23 (88.5)	16 (61.5)	7.706	**0.021**[a,b]
Bruise present, n (%)	3 (11.5)	3 (11.5)	10 (38.5)		
72nd hour					
No bruise (<2 mm), n (%)	24 (92.3)	23 (88.5)	21 (80.8)	1.606	0.448
Bruise present, n (%)	2 (7.7)	3 (11.5)	5 (19.2)		

χ^2: Chi-square test, [a]: Comparison of 2-minute cold application group and control group, [b]: Comparison between 5-minute cold application group and control group

Table 4. Bruise size at 48th and 72nd hours by groups

	2-minute cold application (n=26)	5-minute cold application (n=26)	Controls (n=26)	χ^2	p
Bruise size (mm) at 48th hour, mean±SD, median (min-max)	4.00±1.73, 5.0 (2-5)	10.00±5.00, 10.0 (5-15)	15.00±7.07, 10.0 (10-30)	7.805	**0.020**[a]
Bruise size (mm) at 72nd hour, mean±SD, median (min-max)	4.00±1.41, 4.0 (3-5)	24.33±22.50, 15.0 (8-50)	15.60±9.32, 10.0 (8-30)	4.476	0.107

χ^2: Kruskal-Wallis test, [a]: Comparison between 2-minute cold application group and control group.
SD: Standard deviation, min-max: Minimum-maximum

(1,8,9,11,15,34,35). In this study, the groups subjected to cold application demonstrated lower pain scores than the groups not subjected to cold application. This can be explained by reduced pain perception due to the physiological effects of cold application. Similar to our results, many studies have reported that pain perception decreased in patients who received cold application before SC LMWH injection (1,8,19,20).

In this study, we observed a significant increase in the frequency of bruising in the control group that did not receive cold treatment. Cold application reduces skin and SC tissue temperatures, resulting in vasoconstriction. The vasoconstrictive response initially occurs through direct action and subsequently through a reflex mechanism. When a person is exposed to cold, alpha (α) receptors that modulate vasoconstriction are stimulated by the sympathetic nervous system, leading to vasoconstriction and diminished blood flow to the affected area. Reduced transportation of oxygen and other metabolites to tissues and elimination of waste products ultimately slow down tissue metabolic processes. Thus, the reduction in blood flow induced by vasoconstriction forms the fundamental rationale for cold application to control hemorrhage (11,30,36,37). The reduction in bruising observed in the intervention groups can be attributed to the aforementioned physiological effects of cold application.

Another important result of this study is that the physiological effects of a 2-minute cold application may reduce bruise size. Additionally, although not statistically significant, an increase in bruise size was observed in the 5-minute cold application group compared with the 2-minute cold application group. The influence of cold on blood vessels initially triggers vasoconstriction, but if the skin temperature drops excessively, this vasoconstriction gives way to vasodilation. Vasodilatation reduces the effect of cold at the cellular level (36). Several studies indicated that blood flow tends to decrease after 5 minutes of cold application and further decreases with prolonged applications. However, over time, the body initiates a response known as the “Hunting Reaction” leading to increased skin blood flow to warm the cold tissue (11,38,39). Increased bruise size observed in the 5-minute cold application group compared with the 2-minute cold application group can be explained by the transition from vasoconstriction to vasodilation to increased body temperature and the potential enlargement of bruises due to increased tissue perfusion (39). However, further studies are required to address this issue.

In this study, no hematoma was detected in any groups at 48 and 72 hours. Before commencing the study, we thoroughly reviewed the literature and developed a standardized injection technique for SC LMWH administration that was consistently applied to all patients. The absence of hematoma in the group that did not receive cold application suggests that the standardized injection technique can effectively prevent hematoma. Kuzu and Ucar (1) also concluded that standardized injection technique was an important factor in hematoma prevention.

In this study, participants were randomly selected taking into account factors such as age and gender that were considered to induce pain, bruising, and hematoma at the injection site. In addition, bruising and hematoma assessment was performed by a nurse who was unaware of the method used. This increases the reliability of the study.

The participants were administered only one SC LMWH injection, and the results were limited to the applications to the abdominal region. Furthermore, future studies with different injection sites and number of injections are required.

Conclusion

In conclusion, this study showed that 2 and 5 minutes of cold application before SC LMWH injection effectively reduced pain and bruising frequency, but 2 minutes of cold application was more effective than 5 minutes in reducing bruising size.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the Keçiören Training and Research Hospital (decision no: 2012-KAEK-15/1257, date: 11.01.2017).

Informed Consent: Written informed consent was obtained from each participant.

Authorship Contributions

Concept: C.İ.B., F.İ.Ç., Design: C.İ.B., F.İ.Ç., Data Collection or Processing: C.İ.B., Analysis or Interpretation: C.İ.B., F.İ.Ç., Literature Search: C.İ.B., F.İ.Ç., Writing: C.İ.B., F.İ.Ç.

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Comparison of the effectiveness of an oral combination of thiamine, pyridoxine, and cyanocobalamin with parenteral cyanocobalamin in adolescents with nutritional vitamin B12 deficiency

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Keywords: Vitamin B12, deficiency, adolescent, cyanocobalamin, treatment

ABSTRACT

Aims: Nutritional vitamin B12 deficiency remains a significant public health issue. This study aimed to compare the efficacy of an oral combination of thiamine, pyridoxine, cyanocobalamin, and parenteral cyanocobalamin treatment among adolescents with nutritional vitamin B12 deficiency.

Methods: This retrospective study included patients aged 12-18 years who applied to University of Health Sciences Türkiye, Gülhane Training and Research Hospital General Pediatrics Polyclinic between 2018 and 2019, and serum vitamin B12 levels were measured before and after parenteral or oral combination of thiamine, pyridoxine, and cyanocobalamin treatment.

Results: Of the subjects with post-treatment serum vitamin B12 levels above the target level of 200 pg/mL, parenteral cyanocobalamin was given to 34 patients with a median age of 16 years [interquartile range (IQR), 14 to 16 years], and girls (52.9%), and oral cyanocobalamin was given to 51 patients with a median age of 15 years (IQR, 13 to 16 years), and girls (58.8%). The mean serum vitamin B12 levels before parenteral and oral cyanocobalamin treatment were 150.32±6.49 pg/mL parenteral and 132.35±4.67 pg/mL in oral replacement groups ($p>0.05$). The mean serum vitamin B12 levels after parenteral and oral cyanocobalamin treatments were 566.0±62.77 pg/mL and 463.1±36.97 pg/mL, respectively ($p>0.05$). Both parenteral and oral cyanobalamin treatments caused a significant increase in serum vitamin B12 levels compared with before treatment ($p<0.001$ for both).

Conclusions: In adolescents with nutritional vitamin B12 deficiency, an oral combination of thiamine, pyridoxine, and cyanocobalamin may be preferred to parenteral cyanocobalamin because it is non-invasive and provides an increase in serum vitamin B12 levels similar to parenteral cyanocobalamin treatment.

Introduction

Vitamin B12 deficiency remains a prevalent public health concern in developing countries (1). This deficiency can be attributed to various factors, including malabsorption (as observed in pernicious anemia), congenital anomalies in transport and metabolism, and dietary insufficiency stemming from the body's inability to synthesize vitamin B. In breastfed infants, the root cause of vitamin B12 deficiency often lies in maternal vitamin B12 insufficiency (2); conversely, in older age cohorts, it primarily stems from inadequate consumption of animal-derived foods, resulting in nutritional deficiency. This deficiency is associated with the onset of various medical conditions, including hematological disorders like megaloblastic anemia, along with gastrointestinal and neurological ailments. Although parenteral cyanocobalamin administration is a conventional treatment method for vitamin B12 deficiency, the most crucial disadvantage is that it is invasive. Parenteral cyanocobalamin is a viable option across various pediatric age groups with vitamin B12 deficiency, whereas oral cyanocobalamin is restricted to patients aged 12 years and above because it is available in tablet form combined with thiamine and pyridoxine. Oral and parenteral cyanocobalamin treatments have been reported in the literature in adults with megaloblastic (3), infants of mothers with vitamin B12 deficiency, and children with megaloblastic anemia (4); however, a limited number of studies have been performed on the use of oral cyanocobalamin in the treatment of nutritional vitamin B12 deficiency in adolescents (5-7). Therefore, we aimed in the present study to compare the effectiveness of oral combined cyanocobalamin therapy with that of parenteral cyanocobalamin therapy in adolescents with nutritional vitamin B12 deficiency.

Methods

Study design and participants

This retrospective study included patients of 12-18 years who were admitted to the Pediatric Outpatient Clinics of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital between 2018 and 2019. The main inclusion criteria were pre-treatment serum vitamin B12 levels <200 pg/mL (8), prescription of cyanocobalamin replacement following measurement, and post-treatment serum vitamin B12 level measurement 1 month after treatment. Patients aged younger than 12 years, with post-treatment vitamin B12 levels <200 pg/mL, who were on ongoing cyanocobalamin replacement at the time of screening, with megaloblastic anemia, severe neurological symptoms, malabsorption, iron deficiency anemia, and folate deficiency were excluded. When other causes of deficiency were eliminated, the patient was considered to have nutritional vitamin B12 deficiency. Age- and sex-adjusted anemia was defined according to the World Health Organization criteria (9). Iron and folate deficiency was defined as ferritin and folate levels below 12 and 5 ng/mL, respectively. The study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval number: 2020-51, date: 25.02.2020).

Treatment protocol

As part of the existing outpatient protocol of the clinic, the cases included in the study were administered intramuscular (IM) cyanocobalamin (Dodex® ampules Deva Drug Corporation, Türkiye; 1 mL; 1000 mcg cyanocobalamin) at a dose of 100 mcg every day for a week (it was prepared by diluting 1 mL of medicine with 9 mL of physiological serum and withdrawing it into a 1 mL syringe), 1000 mcg every other day for a week, then 1000 mcg twice a week for a week, and finally 1000 mcg once a week (10). The subjects were prescribed a daily combined tablet (Apikobal® tablet, Santa Farma Drug Corporation, Türkiye) (10) containing 1 mg cyanocobalamin, 50 mg thiamine, and 250 mg pyridoxine. Oral or parenteral treatment is chosen based on the preference of the physician who evaluates the patient in the outpatient clinic. Serum vitamin B12 levels were available in all patients at the time of diagnosis and at the first month of treatment. During the study period, serum vitamin B12 levels were measured using the chemiluminescence method, a Beckman Colter DxI 800 auto-analyzer (Beckman Colter, Brea, CA, USA) at the institution of the work.

Outcomes

The primary outcome was the post-treatment difference in serum vitamin B12 levels among patients who received an oral combination of thiamine, pyridoxine, cyanocobalamin, and parenteral cyanocobalamin treatments.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism v.8.2.0. The Kolmogorov-Smirnov test was used to evaluate the conformity of the data to a normal distribution. Serum vitamin B12 levels were tested using two-way repeated measures analysis of variance (factors "treatment" and "evaluation times (before and after treatment)" and Bonferroni's multiple comparisons test. The significance level was set as at least $p<0.05$. Continuous variables were presented as means and standard error mean (SEM) while categorical variables were reported as frequencies and percentages. The significance level was set as at least $p<0.05$.

Results

Basic characteristics

The study included 85 patients with a median age of 15 [interquartile range (IQR), 14 to 16 years], girls (55.3%) with post-treatment serum vitamin B12 levels above the target level of 200 pg/mL. No biochemical findings of iron or folic acid deficiencies were noted. Parenteral cyanocobalamin was given

administered to 34 patients with a median age of 16 years (IQR, 14 to 16 years), and girls (52.9%), and oral cyanocobalamin were given to 51 patients with a median age of 15 years (IQR, 13 to 16 years), and girls (58.8%). There were no differences in the male and female rates in both groups.

Treatment results

The mean serum vitamin B12 levels before parenteral and oral cyanocobalamin treatment were 150.32±6.49 pg/mL and 132.35±4.67 pg/mL, respectively. The mean serum vitamin B12 levels after parenteral and oral cyanocobalamin treatment were 566.0±62.77 pg/mL and 463.1±36.97 pg/mL, respectively. According to the two-way repeated analysis of variance, the effects of group ($F_{1,83}$=3.258; p=0.0747) and group x time interaction ($F_{1,83}$=1.504; p=0.2235) were not statistically significant. Both parenteral and oral cyanobalamin treatments caused a significant increase in serum vitamin B12 levels in our patients compared with before treatment (p<0.001 for both) (Table 1). There was a significant difference in the time results ($F_{1,83}$=6116.3; p<0.001). Subsequently, in the post-hoc analysis performed with the Bonferroni test, no significant difference was observed between the two groups in terms of vitamin B12 levels before and after treatment (p=0.9961, p=0.068, respectively). Changes in serum vitamin B12 levels before and after treatment in the oral and parenteral cyanocobalamin treatment groups are shown in Figure 1.

No safety issue was recorded in patient files.

Discussion

Dietary deficiency is the primary cause of vitamin B12 deficiency (11), which results from insufficient consumption of animal-based foods. Vitamin B12 deficiency is also observed in breastfed infants with mothers experiencing vitamin B12 deficiency, pregnant women, and older vegetarian and vegan children who have limited intake of animal-based foods (12). Methylcobalamin, hydroxycobalamin, adenosylcobalamin, and cyanocobalamin are viable treatments for vitamin B12 deficiency. In parenteral vitamin B12 replacement, hydroxycobalamin and cyanocobalamin are administered IM. Alternatively, ampoules containing cyanocobalamin alone or combined with thiamine, pyridoxine, methylcobalamin, or adenosylcobalamin can be administered orally. There are also recommendations for the combined use of these different forms of cobalamin in the treatment of vitamin B12 deficiency (13).

Cyanocobalamin is the most widely used agent for treating vitamin B12 deficiency and can be administered via parenteral or oral routes. In conditions like pernicious anemia, a well-established dosing regimen involves an initial dose of 100 mcg/day for 1 week and a dose of 1000 mcg/day on alternate days for another week. Subsequently, the recommended dosage is 1000 g/day twice a week for one week, and finally, 1000 g/day once a week (10). Oral cyanocobalamin recommendations include daily tablets containing 1000 g of cyanocobalamin, 50 mg of thiamine, and 250 mg of pyridoxine. Alternatively, for patients unable to swallow tablets or those under six years of age, daily oral administration of ampoules containing 1000 mcg of cyanocobalamin is recommended (10). Oral cobalamin is cost-effective, safe, and convenient (14).

In children, parenteral vitamin B12 is the established treatment for megaloblastic anemia (4), neuropsychiatric disorders, absorption disorders (15,16), and metabolic disorders. Unfortunately, no standard protocol exists for oral replacement therapy to address nutritional vitamin B12 deficiency resulting from insufficient dietary intake without an underlying pathology. Parenteral therapy has several drawbacks, including elevated treatment costs, reduced efficacy, and complicated administration.

Few studies have explored the equivalentity of oral versus parenteral cyanocobalamin in the replacement therapy for

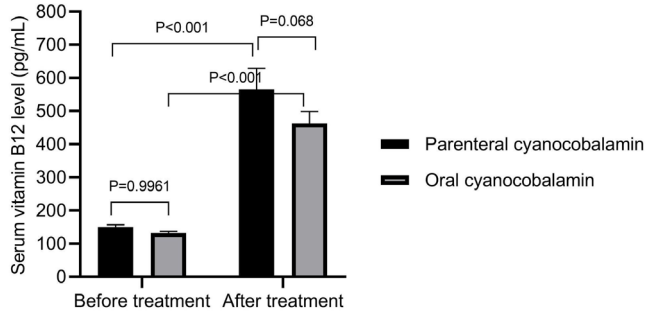

Figure 1. Changes in serum vitamin B12 levels before and after oral and parenteral cyanocobalamin treatment

Table 1. Comparison of serum vitamin B12 levels before and after parenteral and oral cyanocobalamin therapy among adolescents with vitamin B12 deficiency

Administration routes of cyanocobalamin	Before treatment (pg/mL)[e]	After treatment (pg/mL)[e]	p[Ω] value
Parenteral (n=34)	150.32±6.49	566.0±62.77	**p<0.001**
Oral (n=51)	132.35±4.67	463.1±36.97	**p<0.001**
p[Ω] value	0.9961	0.068	

[Ω]Bonferroni's multiple comparison p value.
[e]The results are expressed as mean±SEM.
SEM: Standard error of the mean

nutritional vitamin B12 deficiency among pediatric patients. Sezer et al. (10) compared the effectiveness of oral and IM cyanocobalamin in this pediatric population. Their prospective study involved 142 children, among whom 82 received oral and 60 IM cyanocobalamin. Children with serum cobalamin levels below 300 pg/mL received either parenteral or oral cyanocobalamin therapy. IM cyanocobalamin (1000 mcg) was administered at daily doses of 100 mcg for one week, followed by 1000 mcg/day on alternate days for the subsequent week, 1000 mcg/day twice a week for one week, and ultimately once a week. Mean serum cobalamin levels showed a notable increase from a pre-treatment level of 183.5±47 pg/mL to 482±318.9 pg/mL in the oral cyanocobalamin group and from 175.5±42.5 pg/mL to 838±547 pg/mL in the parenteral treatment group ($p<0.001$). Before treatment, 82 children developed anemia according to age and gender. After treatment, 14/41 and 8/41 patients still had anemia in the parenteral and oral arms, respectively. There was no significant change in the number of patients who still had anemia at the end of the first month of treatment in the parenteral and oral treatment groups. The oral and parenteral formulations successfully restored serum vitamin B12 levels to the normal range. Although vitamin B12 levels before parenteral and oral cyanocobalamin treatment were statistically similar to those in this study, the patients did not have anemia. The mean serum vitamin B12 level significantly increased after treatment, and there was no significant between-group difference. In the study by Sezer et al. (10), the research group included individuals aged 1 month to 18 years, and cyanocobalamin was provided in oral ampoules for those unable to swallow tablets and for the subgroup under six years of age. In contrast, our study focused on patients aged 12-18 years, and the cyanocobalamin used was in tablet form combined with thiamine and pyridoxine.

Bahadir et al. (17) investigated the efficacy of oral vitamin B12 supplementation in children with nutritional vitamin B12 deficiency. Their study involved 47 children aged 1 month to 17 years having serum vitamin B12 levels below 200 pg/mL. They categorized the participants into two main groups: Group 1 (1-20 months) and Group 2 (6-17 years). Subsequently, they further divided the patients into subgroups based on the duration of treatment, resulting in Groups 1A and 2A (4 months of treatment) and Groups 1B and 2B (8 months of treatment). All participants were administered 1000 µg of oral cyanocobalamin daily during the first week, every other day during the subsequent two weeks, twice a week for the subsequent two weeks, and finally once a week. The administration of high oral vitamin B12 doses significantly improved serum vitamin B12 levels in all groups, with the regimen being more effective in Group 1A and Group 1B. The correlation analysis between serum vitamin B12 levels and age at the end of treatment indicated a decreasing trend with increasing age. They found that a 4-month oral vitamin B12 supplementation (1000 µg) effectively managed nutritional vitamin B12 deficiency in children. However, dose adjustments based on body weight among older children are necessary (15). On the other hand, their study included patients aged 1 month to 17 years who received oral cyanocobalamin for 4 months, whereas our study included a population aged 12-18 years who received oral or parenteral treatment during a 4-week observation.

Tuğba-Kartal and Çağla-Mutlu (18) aimed to compare the efficacy of sublingual (SL) cyanocobalamin and methylcobalamin with IM cyanocobalamin treatment in children aged 5-18 years with vitamin B12 deficiency. They found that SL and methylcobalamin were equally effective as IM cyanocobalamin in improving serum vitamin B12 levels and addressing hematologic abnormalities. In our study, oral cyanocobalamin in tablet form showed a similar effectiveness trend, though the patient age was different.

Orhan Kiliç et al. (19) compared the efficacy of oral, SL, and IM vitamin B12 supplementation in children aged 0-3 years. They concluded that SL methylcobalamin was as effective as oral and IM cyanocobalamin in improving serum vitamin B12 levels in this age group. While SL methylcobalamin and SL cyanocobalamin have gained popularity in treating nutritional vitamin B12 deficiency, oral cyanocobalamin retains its significance due to its cost-effectiveness. In our study, methylcobalamin was not used, and the adolescent group was considered; however, oral cyanocobalamin increased serum vitamin B12 levels, similar to IM cyanocobalamin, in the adolescent group.

A Cochrane review by Wang et al. (3) indicated that oral and IM cyanocobalamin exhibited similar effects on normalizing serum vitamin B12 levels. The study results suggested that the assumption of oral cyanocobalamin's safety over IM vitamin cyanocobalamin was grounded in low-evidence studies. Consequently, high-quality research is imperative in this area. In our study, there are no safety issues related to oral and parenteral cyanocobalamin.

Our study has several limitations, including a low sample size, lack of measurement of methylmalonic acid and homocysteine levels, and absence of detailed nutritional history. A short follow-up of 4 weeks also requires confirmation of long-term.

Conclusion

In conclusion, this study found that daily oral cyanocobalamin treatment raised serum vitamin B12 levels to the normal range, similar to parenteral cyanocobalamin treatment for nutritional vitamin B12 deficiency in adolescents. Given its non-invasive, cost-effective, and user-friendly features, oral vitamin B12 administration should be encouraged, especially for parents seeking to avoid painful injections for their children. Nevertheless, further comprehensive research is warranted to confirm the long-term maintenance of serum vitamin B12 levels in this age group.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval number: 2020-51, date: 25.02.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.G., Concept: Ö.G., M.A., E.A., Design: Ö.G., M.A., E.A., Data Collection or Processing: Ö.G., M.A., Y.H.A., B.Ö.G., Analysis or Interpretation: M.A., F.Ü., Literature Search: Ö.G., Writing: Ö.G.

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Relationship between glycemic control and oral health status in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Diabetes mellitus (DM) is associated with dry mouth, reduced saliva, taste changes, and periodontal disease. This study aimed to evaluate and determine the correlation between oral health status and glycaemic control levels in patients with type 2 DM (T2DM).

Methods: This cross-sectional study was conducted on patients with T2DM aged 35-65 years. Glycemic control levels were categorized as good control (≤7% of HbA1c) and poor control (>7% of HbA1c). Full mouth plaque score (FMPS), full mouth bleeding score (FMBS), probing depth (PD), and clinical attachment level (CAL) were determined, along with xerostomia (using a standard questionnaire) and hyposalivation (using modified Schirmer test, MST).

Results: This study included 70 individuals with T2DM, comprising 49 males (70%) and 21 females (30%) with a mean age of 55.36±8.3 and 49.36±6.8 years, respectively. Among those with poor glycemic control, a significantly higher prevalence of xerostomia (52.2%), hyposalivation (47.8%), and periodontitis (moderate; 47.8% and severe; 21.7%) was observed compared with those with good control (p=0.027, 0.001, 0.007, respectively). HbA1c exhibited a significant moderate positive correlation with FMPS (r=0.447; p=0.001) and a low correlation with FMBS (r=0.283; p=0.018) and CAL (r=0.301; p=0.011).

Conclusions: The study concluded that individuals with poor glycemic control for T2DM have a higher incidence of xerostomia, hyposalivation, and compromised periodontal health, resulting in a decline in their oral health status.

Introduction

The development of type 2 diabetes mellitus (T2DM), a common metabolic disorder worldwide, is primarily driven by two key factors: dysfunctional insulin secretion from pancreatic β-cells and the resistance of insulin-sensitive tissues to insulin action (1). Periodontitis is an inflammation-induced disease affecting the supportive tissues of teeth. It is caused by specific microorganisms or groups of closely related microorganisms, leading to the gradual destruction of the periodontal ligament and alveolar bone, accompanied by increased probing depth (PD), gingival recession, or both (2). Periodontitis is the sixth consequence of diabetes mellitus (DM), and both type 1 DM (T1DM) and T2DM are significant risk factors for periodontal disease (3). Patients with T2DM may be more susceptible to or experience a more severe periodontal disease if they have poor glycemic control. Moreover, periodontitis has a systemic link with adverse cardiovascular outcomes. Furthermore, subsequent tooth loss associated with periodontitis can lead to deleterious dietary modifications, potentially worsening comorbidities in patients with T2DM (4).

Saliva, the main environment for oral flora, mechanically cleanses the remnants of nonadherent bacteria and other debris from the mouth (5). Certain medications, head and neck radiation therapy, Sjögren's disease, and other systemic conditions, including DM, may reduce salivary flow. The diabetic condition associated with prolonged hyperglycemia can infer salivary gland function and influence the amount and nature of saliva produced (6). The subjective feeling of mouth dryness is known as xerostomia (7). Of the patients with DM, 10-30% exhibit xerostomia, a condition characterized by decreased saliva production (8). Hypofunction of the salivary glands can cause changes in the oral mucosa, including elevated concentrations of glucose and mucin, a reduction in the generation of antimicrobial agents, loss of taste perception, halitosis, periodontal disease, dental caries, inefficient wound healing, and a predisposition to oral mucosal disease (9). Saliva's wide range of antibacterial agents, antibodies, and buffers gives it a protective role; hence, periodontal health can deteriorate by a decrease in its flow rate (10). Given the significant burden of oral diseases and their association with DM, oral health problems contribute to pain, impaired mastication, and xerostomia, significantly impacting the overall quality of life, loss of work productivity, and high treatment costs (11,12). Nevertheless, oral health is still a neglected and underestimated health concern globally (13). Hence, the present study aimed to assess and correlate the oral health status and glycemic control level of patients with T2DM.

Methods

Study design and patient selection

In this cross-sectional study, patients who applied to the Department of Periodontics at AB Shetty Memorial Institute of Dental Sciences, Mangalore, Karnataka, underwent screening and clinical examinations between July 2022 and June 2023. Patients in the age group of 35 to 65 years, medically diagnosed with T2DM for the past five years with good glycemic control ≤7% of glycated hemoglobin (HbA1c), and poor glycemic control of >7% of HbA1c, with a minimum complement of 20 natural teeth, were included in the study (14). Patients diagnosed with any systemic illness other than T2DM and those under medication that affects the periodontium (such as antiepileptic drugs and immunosuppressants), those who underwent periodontal therapy three months before the study, smokers, and pregnant or nursing women were excluded. The study was approved by the AB Shetty Memorial Institute of Dental Sciences Institutional Ethics Committee (ref. no: ETHICS/ABSMIDS/269/2022, date: 25.06.2022) and was conducted in compliance with the principles outlined in the Helsinki Declaration, revised in 2013. Written informed consent was obtained from the participants.

Data collection

Demographic and clinical data

Standard demographic data, including age, sex, and body mass index (BMI), were collected using a standardized proforma for the participants. Glycemic control was estimated based on HbA1c values. Participants without an HbA1c report within the past three months of the study were referred to the institution's medical center for HbA1c level measurement.

Assessment of oral health

Oral and periodontal health was assessed using the following parameters: Oral hygiene status was evaluated using the full mouth plaque score (FMPS) (15). The full mouth bleeding score (FMBS), PD, and clinical attachment level (CAL) were measured with a marked periodontal probe (UNC-15 probe, Hu-Friedy, Chicago, IL, USA) (16,17). All teeth were probed at six sites: mesio-lingual, mid-lingual, disto-lingual, mesiobuccal, mid-buccal, and distobuccal. Plaque and bleeding scores were based on the absence or presence of plaque and bleeding, respectively.

Salivary flow and xerostomia assessment

The unstimulated salivary flow rate was assessed using the MST (Schirmer strips®). This strip was adapted from the Schirmer tear test commonly used by ophthalmologists. Patients were instructed to sit upright in a dental chair, swallow all saliva before the test, refrain from swallowing during the test, and rest their tongue on the hard palate. Using a cotton plier, the MST strip was held vertically with the rounded end at the floor of the mouth on either side of the lingual frenum. The wetness of saliva ascended the strip upon contact with the round end, and its distance was measured at 1, 2, and 3 min, with the readings promptly recorded. If the strip's moisture content was <25 mm after three minutes, hyposalivation was considered (18). A 10-item questionnaire on the experience of xerostomia was used (19). Xerostomia is considered present if the patient responds positively to one or more of the following questions: Do you feel your mouth dry when you eat? Do you have difficulty swallowing food? Do you need to drink while eating? Do you feel like the amount of saliva in your mouth is too low most of the time? (adapted according to Fox criteria) (20,21).

Statistical Analysis

The collected data were analyzed using nMaster software version 2. For scale variables, data were expressed as mean and standard deviation, and for categorical variables, data were expressed as frequency percentages. The chi-square test was employed to compare xerostomia, hyposalivation, and periodontal status with glycemic control levels in patients with T2DM. Pearson's correlation was used to assess the correlation

between HbA1c and the clinical variables FMPS, FMBS, and CAL. P values less than 0.05 were considered statistically significant.

Results

Seventy patients with T2DM, comprising 49 males (70%) and 21 females (30%), participated in the study. The mean age of the participants was 53.7±8.3 years (males 55.3±8.3 and females 49.3±6.8 years, respectively). As shown in Table 1, the participants had a mean HbA1c level of 6.9±0.9 % among patients with T2DM. Notably, most participants exhibited good glycemic control (67.4%), with 32.8% demonstrating poor glycemic control. The mean PD and CAL were 2.8±1.5 mm and 4±1.5 mm, respectively. Over half (67.1%) of the T2DM patients exhibited good glycemic control. Gingivitis was present in 50% of the participants, and the remaining population had moderate-to-severe chronic periodontitis (41.4% and 8.6%, respectively). Xerostomia was reported in 65.7% of participants, whereas hyposalivation was present in only 20% of the population.

Among the participants with poor glycemic control, approximately 52.2% had xerostomia, whereas only one-fourth (24.5%) of participants with good glycemic control reported xerostomia, and the difference was statistically significant (p=0.027). Additionally, it was observed that among the T2DM individuals with poor glycemic control, approximately 47.8% had hyposalivation, whereas among those with good control, only 6.4% exhibited hyposalivation, and the distribution was statistically significant (p=0.001). Within the group of individuals exhibiting poor glycemic control, 47.8% and 21.7% had moderate and severe periodontitis, respectively. Conversely, among participants with optimal glycemic control, 59.6% developed gingivitis, whereas only 2.1% developed severe periodontitis. This distribution was statistically significant (p=0.007) (Table 2).

Table 1. Demographic and clinical characteristics of the study population

Age, years, mean±SD	
Male	55.3±8.3
Female	49.3±6.8
Overall	53.7±8.3
Sex, n (%)	
Male	49 (70)
Female	21 (30)
BMI, kg/m^2, mean±SD	
Male	25.1±5.8
Female	23.0±4.3
Overall	23.2±4.9
HbA1c, %, mean±SD	6.9±0.9
FMPS, %, mean±SD	38.7±5.3
FMBS, %, mean±SD	20.1±6.1
PD, mm, mean±SD	2.8±1.5
CAL, mm, mean±SD	4±1.5
Glycemic control, n (%)	
Good	47 (67.1)
Poor	23 (32.8)
Periodontal status, n (%)	
Gingivitis	35 (50)
Moderate periodontitis	29 (41.4)
Severe periodontitis	6 (8.6)
Xerostomia, n (%)	24 (34.3)
Hyposalivation, n (%)	14 (20)

SD: Standard deviation, BMI: Body mass index, HbA1c: Glycated hemoglobin, FMPS: Full mouth plaque scores, FMBS: Full mouth bleeding scores, PD: Probing depth, CAL: Clinical attachment level, n: Number, %: Percentage

Correlation of glycemic control with clinical variables

HbA1c had a moderate positive correlation with FMPS that was statistically significant (r=0.447; p=0.001) and a low degree of correlation with FMBS (r=0.283; p=0.018) and CAL (r=0.301; p=0.011), respectively (Pearson's correlation, statistically significant at p<0.01 and p<0.05).

Discussion

The sensation of having a dry mouth (xerostomia) is one of the most prevalent symptoms of DM (22). Hyperglycemia and diabetic neuropathy in uncontrolled T2DM can lead to xerostomia because excessive glucose is converted into sorbitol, damaging nerve cells and causing abnormalities in salivary secretion (23). The onset and progression of numerous symptoms and oral manifestations are significantly influenced by glucose regulation (24).

In this regard, the present study illustrated that the prevalence of xerostomia was higher in patients with T2DM who had poor glycemic control than those with good glycemic control. In support of the present study, an investigation by Shrivastava et al. (25) reported that individuals with T2DM exhibited a higher prevalence of xerostomia with increased HbA1c levels. However,

Table 2. Distribution of clinical conditions of the study participants based on the glycemic control levels

Clinical conditions		Glycemic control		p value
		Good	Poor	
Xerostomia, n (%)		12 (25.5)	12 (52.2)	**0.027***
Hyposalivation, n (%)		3 (6.4)	11 (47.8)	**0.001***
Periodontal status	**Gingivitis,** n (%)	28 (59.6)	7 (30.4)	**0.007***
	Moderate periodontitis, n (%)	18 (38.3)	11(47.8)	
	Severe periodontitis, n (%)	1 (2.1)	5 (21.7)	

n: Number, %: *Statistically significant

contrary to the current study findings, another study revealed no significant difference in the incidence of xerostomia reported by patients with controlled and uncontrolled T1DM and T2DM (26). Several pathological alterations, including malfunction of the salivary glands and decreased salivary production, are frequently evident in hyperglycemia (27). The current investigation revealed that patients with poorly controlled T2DM exhibited a higher number of individuals experiencing hyposalivation compared with those with good control. Al-Maweri et al. (26) observed a similar pattern in participants with T1DM or T2DM, but the results were nonsignificant. Additionally, findings from another study suggest a possible association between salivary flow and composition and poor glycemic control in patients with T2DM (28). Conversely, Dodds and Dodds (19) found no noticeable differences in the salivary flow rate of patients with T2DM.

Changes in the salivary glands driven by the detrimental effects of DM can cause a decrease in saliva, which can have adverse consequences like a higher risk of developing periodontal disease and dental caries (29). Moreover, inadequate regulation of glucose levels has been identified as a significant factor contributing to periodontitis (30). The present study revealed a higher prevalence of chronic periodontitis in individuals with T2DM who exhibited inadequate glycemic control compared with those with good glycemic control. Many hypotheses have been established to explain the plausibility of uncontrolled DM and periodontal diseases, such as host response alterations, collagen metabolism, and vascularity (31). Similarly, Awartani (32) showed an increased mean CAL in individuals with poor glycemic control compared with those with good glycemic control. Hence, the negative impact of T2DM on periodontal health increases with poorer glycemic control.

Notable alterations in poorly controlled DM include diminished defense mechanism and vulnerability to infections, ultimately resulting in destructive periodontal disease (33). Elevated glucose levels in the gingival fluid and bloodstream in individuals with DM may cause qualitative shifts in bacteria, potentially worsening the severity of periodontal disease in those with poorly controlled DM (34).

In this regard, in the current study, participants with poorly controlled T2DM had a higher number of individuals with severe periodontitis than those with good glycemic control. These results align with observations from another study, in which patients with poorly controlled T2DM had a higher prevalence of severe periodontitis (2.5%) than those with normal or good glycemic control (0%) (35). However, contrary to this, a study in an Indonesian population found no correlation between any measure of periodontitis severity and HbA1c levels in individuals with T2DM. The authors outlined several factors, such as diverse medications for blood sugar control, the potential impact of BMI on insulin resistance, and ethnic variations across different study populations, for the absence of a relationship between HbA1c and periodontitis severity (36).

The current study findings corroborate those reported by Kumar et al. (2013) (37), who observed an association between good oral hygiene and lower HbA1c levels in patients with T2DM. Qureshi et al. (2020) (38) found a significant correlation between periodontal parameters and HbA1c levels in patients with T2DM, similar to the present findings. Another cross-sectional study further substantiated the findings of the current study. The study revealed that participants with T2DM and poor glycemic control exhibited higher mean plaque, bleeding, and CAL (39).

Study Limitations

The main limitation of this study is that it only included a convenience sample of patients with DM from a particular institution. Consequently, these findings may not be fully generalizable to individuals with diabetes in other geographic regions. Future longitudinal studies are warranted to explore causality and better understand the dynamics over time. Second, the questionnaire we used to determine xerostomia was subjective. Third, we were not able to evaluate socioeconomic status, including occupation and education level, the frequency of dental checkup visits, and awareness of the connections between oral and systemic diseases that determine oral health.

Conclusion

The study concluded that individuals with poor glycemic control for T2DM have a higher incidence of xerostomia, hyposalivation, and compromised periodontal health, resulting in a decline in their oral health status. These findings suggest that poor glycemic control negatively impacts oral health. More comprehensive observational studies are required to explore oral health concerns and associated factors among individuals with T2DM.

Ethics

Ethics Committee Approval: The study was approved by the AB Shetty Memorial Institute of Dental Sciences Institutional Ethics Committee (ref. no: ETHICS/ABSMIDS/269/2022, date: 25.06.2022) and was conducted in compliance with the principles outlined in the Helsinki Declaration, revised in 2013.

Informed Consent: Written consent was obtained from the participants, who were informed about the study objectives.

Authorship Contributions

Concept: B.A.K., N.S., A.S., Design: B.A.K., N.S., A.S., Data Collection or Processing: B.A.K., K.S.C., Analysis or Interpretation: B.A.K., N.S., Literature Search: B.A.K., N.S., K.S.C., Writing: B.A.K., N.S., K.S.C.

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Relationship between dietary histamine intake and clinical parameters in Behçet syndrome

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ABSTRACT

Aims: This study investigated histamine intake and its associations with clinical and biochemical findings in patients with Behçet syndrome.

Methods: Patients with Behçet syndrome were prospectively enrolled using a cross-sectional, multicenter, and online survey design. Sociodemographic parameters, including age, gender, smoking and alcohol intake, nutritional counseling history, anthropometric measurements, clinical characteristics, and biochemical results, were obtained using an online questionnaire. Dietary histamine intake was determined using a food frequency questionnaire.

Results: The study included 66 patients (mean age: 37.5±11.3 years, women: 53%. Food consumption was reported to trigger oral aphthae in 81% of the individuals, and the most frequently reported triggers were eggplant (37.5%), tomatoes (37.5%), and citrus fruits (34.3%). There was a significant positive correlation between dietary histamine intake and white blood cell counts (r=0.650; p=0.050). There were no significant differences in the clinical characteristics, including oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal system involvement, joint involvement, and vascular involvement between patients with low and high dietary histamine intake. A positive correlation was found between dietary histamine intake and the frequency of attacks (r=0.324; p=0.008).

Conclusions: This study showed that increased dietary histamine intake was associated with an increased frequency of attacks in patients with Behçet syndrome. Oral aphthae are associated with certain foods, such as eggplant, tomatoes, and citrus fruit.

Introduction

Behçet syndrome is a recurrent inflammatory multiorgan syndrome affecting the skin, mucosa, eyes, joints, gastrointestinal tract, and central nervous system, and is characterized by diverse clinical presentations (1). Oral and genital ulcers are common in Behçet syndrome and typically manifest as initial symptoms (2). In severe cases, gastrointestinal and/or central nervous system symptoms, known as neuro-Behçet symptoms, may occur (3). The etiology of Behçet syndrome remains unclear. It is considered an autoinflammatory and autoimmune trait triggered by genetic or infectious factors in genetically predisposed and susceptible individuals (2). Although disease flares in Behçet syndrome cannot be estimated, various potential triggers, including nutrients, stress, mucosal trauma, menstruation, tooth extraction, and infections, have been reported (4). Given the rarity of Behçet syndrome, no established nutritional protocol specific to this condition exists. However, the nutritional status of patients is influenced by the clinical presentation of the syndrome, ongoing inflammation, and medication use, given its classification as a chronic inflammatory disorder. Consequently, these factors often induce alterations in appetite, gastrointestinal function, and metabolic status (5). Hence, regular monitoring of nutritional status is of paramount importance.

Histamine, a bioactive amine, is synthesized from histidine via the action of the enzyme L-histidine decarboxylase, which is a process reliant on pyridoxal phosphate (6). It is notable for its role as a mediator possessing proinflammatory properties, influencing the activity of various immune cells, such as T and B lymphocytes, neutrophils, eosinophils, basophils, macrophages, dendritic cells, and endothelial cells. Histamine is naturally present in certain foods. Histamine is linked to exacerbations of symptoms in Behçet syndrome (7). Several foods have been reported to contribute to increased recurrence rates of oral aphthae, many of which are either histamine-rich, such as ripened cheeses, or histamine-releasing, including nuts, pineapple, citrus fruits, strawberries, tomatoes, peanuts, alcohol, spices, eggplant, and vinegar (4,8). Oral aphthae in Behçet syndrome may be attributed to a mucosal pathergy reaction induced by histamine-rich foods or the degranulation or activation of mast cells triggered by various dietary or non-dietary factors. The prevalence of commonly cited trigger foods rich in histamine or capable of eliciting histamine release suggests a mechanism of hyper-reactivity (7).

Histamine, present in foods at different concentrations, tends to escalate during ripening and fermentation processes (9,10). This upsurge in histamine levels stems from the microbial conversion of amino acids, a process influenced by several factors, including precursor amino acids in foods, freshness, salt content, processing techniques, storage conditions, environmental factors conducive to microbial growth (e.g., temperature and pH), and the activity of bacterial decarboxylases (10). The European Food Safety Authority (EFSA) issued a scientific report in 2011 to outline the average histamine levels in various foods. Food categories with the highest histamine concentrations include dried anchovies (348 mg/kg), fish sauce (196-197 mg/kg), fermented vegetables (39.4-42.6 mg/kg), cheese (20.9-62 mg/kg), other fish and fish products (26.8-31.2 mg/kg), and fermented sausages (23.0-23.6 mg/kg) (11). Beyond histamine-rich foods, certain items, including citrus fruits, nuts, tomatoes, spinach, chocolate, spices, egg whites, various beverages, additives, and medications, are considered to either stimulate histamine release from tissue mast cells (as histamine liberators) or impede the enzyme essential for its degradation (8).

This study aimed to determine the dietary histamine intake of patients with Behçet syndrome and its association with clinical and biochemical markers.

Methods

Study design and participants

This study adopted a descriptive cross-sectional design to present observational data on Behçet syndrome. Participants were enrolled between March 2022 and December 2022 using an online questionnaire hosted on Google Forms. Recruitment efforts were facilitated through social media announcements. Participants hailed from all across the regions in Türkiye and received treatment at different healthcare facilities. The online questionnaire was formulated by drawing upon the methodology of a previous study with a similar design (12). An online questionnaire link was sent to individuals willing to participate. The inclusion criteria were age between 18 and 65 years and a diagnosis of Behçet syndrome by a rheumatologist. The exclusion criteria were histamine intolerance, pregnancy, breastfeeding, and cancer. A power analysis was conducted to determine the required sample size, determining that a minimum of 139 participants was necessary for an effect size of 0.5 at a 95% confidence level and 80% power. However, the study was able to recruit only 66 participants. The study was conducted following the guidelines laid down in the Declaration of Helsinki, and the procedures involving human subjects/patients were approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Code: 2022/06-09 on 19.10.2021).

Data collection

Sociodemographic variables included were age, sex, nutritional counseling history, anthropometric variables, clinical characteristics, biochemical variables, past flares, and dietary histamine intake.

Anthropometric measurements

The weight and height of the participants were self-reported. Participants were informed to measure their weight in the morning on an empty stomach, wearing minimal and light clothing, without shoes, using a 100-g sensitive scale; their height was measured with their feet together and in an upright position, with their head in the Frankfort plane. Body mass index (BMI) was calculated according to the classification provided by the World Health Organization (13,14).

Clinical and biochemical findings

Clinical findings, including oral aphthosis, genital aphthosis, dermatologic lesions, ocular lesions, joint involvement, vascular manifestations, gastrointestinal involvement, and the frequency of flares (i.e., exacerbations of clinical symptoms/findings), were assessed (15). These clinical manifestations were presented in the questionnaire, prompting patients to indicate both specific findings and frequency annually. The clinical findings reported by the participants as flares were recorded based on self-reports.

Because patients were from different regions of Türkiye, the hospital protocols varied. Therefore, patients were requested to manually enter the results of their biochemical findings from their medical records into the questionnaire. The variables were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin level, white blood cell (WBC) count, platelet count, mean corpuscular volume (MCV), red cell distribution width

(RDW), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), iron-binding capacity, and ferritin levels obtained within the preceding six months.

Histamine intake

We assessed dietary histamine intake using a food frequency questionnaire that captured 30 days of food consumption. It was specifically tailored to evaluate histamine intake. A structured food consumption frequency form consisting of 24 items was used to quantify histamine consumption. This study was based on the EFSA publication titled "Panel on Biological Hazards (BIOHAZ). Scientific Opinion on risk-based control of biogenic amine formation in fermented foods" (11). The collected data were processed via the Nutrition Information System to calculate the participants' dietary histamine intake. Given the absence of established cutoff values for low or high histamine intake, we used the median dietary histamine intake as the threshold.

Study endpoints

The primary outcome was the relationship between dietary histamine intake and the frequency of flares. Differences in clinical and biochemical findings between the low and high histamine groups were secondary outcomes.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences statistics for Windows, version 27.0 (IBM Corp., Armonk, NY: USA, 2020). Continuous variables are presented as mean±standard deviation. Qualitative variables are presented as numbers and percentages. The normality of data distribution was determined using the Shapiro-Wilk test. The Mann-Whitney U or Kruskal-Wallis analysis was used to test between-group differences. Chi-square analysis was used to compare categorical data. Correlation analyses were performed using the Spearman test. In all analyses, $p<0.05$ was considered statistically significant.

Results

Descriptive statistics

The study included 66 patients (mean age: 37.5±11.3 years, women: 53%). The mean BMI was 25.3±5.3 kg/m^2, and 6.1% were underweight, 51.5% were normal, 25.8% were overweight, and 16.7% were obese.

The median dietary histamine intake was 886.3 (28.0-6065.9) mg in total, 883.5 (303.6-5321.9) mg in women, and 1092.6 (28.0-6065.9) mg in men. There was no significant difference in dietary histamine intake between men and women (p=0.944). Of the participants, 54.5% believed that food consumption reduced syndrome symptoms. Only 28.8% of the participants received nutritional counseling.

Of the participants, 48.5% experienced symptoms of Behçet syndrome after consuming certain foods. The foods associated with increased symptoms were eggplant (37.5%), tomatoes (37.5%), citrus fruits (34.3%), nuts (31.2%), chocolate (15.6%), dessert (15.6%), dairy products (9.3%), acidic foods and drinks (9.3%), spicy foods (9.3%), sauces (6.2%), strawberries (6.2%), fish (3.1%), bacon (3.1%), fried foods (3.1%), bananas (3.1%), apples (3.1%), and cherries (3.1%). Concerning the symptoms upon consumption of these foods, 81% of the individuals reported oral aphthae, 31.2% experienced a burning sensation in the oral mucosa, 21.9% observed occurrence of new ulcers, 21.9% reported joint involvement, 6.2% indicated experiencing fatigue, 6.2% reported abdominal pain, and 3.1% reported fever.

The frequency of flares increased with BMI, but the relationship was not statistically significant.

Table 1 presents the comparisons of biochemical results according to dietary histamine intake. Notably, WBC counts exhibited a statistically significant increase among patients with higher dietary histamine intake.

Table 2 presents the comparison of clinical diagnoses according to dietary histamine intake. The prevalence rates of oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal, joint, and vascular involvement were 86.4%, 47.0%, 37.9%, 45.4%, 15.2%, 60.6%, and 27.3%, respectively. There was no significant difference in the incidence of oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal involvement, joint involvement, or vascular involvement between the groups with low and high dietary histamine intake (p>0.05).

Table 3 presents the correlation analysis between the frequency of flares, BMI, and dietary histamine intake. Notably, no significant relationship was observed between BMI and the frequency of flares (r=-0.020; p=0.872). However, a statistically significant and positive correlation was found between dietary histamine intake and the frequency of flares (r=0.324; p=0.008).

Concerning the relationship between dietary histamine intake and biochemical findings, a significant positive correlation was found only with the WBC (r=0.650; p=0.05) (Table 4).

Discussion

The findings of this study suggest a notable association between increased dietary histamine intake and a high frequency of flares among patients with Behçet syndrome. Moreover, there was a positive correlation between WBC count and dietary histamine intake. Notably, oral aphthae emerged as the predominant symptom of Behçet syndrome following food consumption, predominantly eggplant, tomato, and citrus fruit.

The inflammatory nature of obesity and the status of body composition impact the severity and activity of chronic

Table 1. Biochemical results according to dietary histamine intake

	Dietary histamine intake <886.3 mg		Dietary histamine intake >886.3 mg		p*
	n	Mean±SD	n	Mean±SD	
Biochemical results					
CRP (mg/dY)	18	20.5±46.8	14	3.9±7.3	0.220
ESR (mm/h)	7	11.0±9.4	10	12.6±13.0	0.887
Hemoglobin (g/dL)	13	13.3±1.4	9	15.7±11.0	0.324
WBC (x10^3/uL)	11	6.6±1.4	6	11.0±6.15	**0.037**
Platelet count (x10^3/uL)	10	269.2±39.9	6	266.7±69.6	0.875
MCV (fL)	11	84.7±6.8	5	90.6±9.53	0.320
RDW (%)	10	17.0±7.8	5	25.8±26.8	1.000
BUN (mg/dL)	7	13.9±6.4	4	12.0±7.84	0.527
ALT (IU/L)	13	30.8±28.0	10	24.4±12.8	0.879
AST (IU/L)	13	25.1±13.6	9	20.4±8.3	0.556
Iron binding capacity (ug/dL)	5	328.0±23.7	5	290.0±111.6	0.151
Ferritin (mY/ng)	6	97.1±186.8	5	26.3±13.7	0.792

*Mann-Whitney U test. Significant p values are shown in bold.
SD: Standard deviation, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 2. Dietary histamine intake and clinical characteristics

	Dietary histamine intake <886.3 mg		Dietary histamine intake >886.3 mg		Total		p*
	n	%	n	%	n	%	
Oral aphthae	28	84.8	29	87.9	57	86.4	0.500
Genital ulcer	13	39.4	18	54.5	31	47	0.162
Uveitis	16	48.5	9	27.2	25	37.9	0.064
Dermatologic lesions	15	45.5	15	45.5	30	45.4	0.597
Gastrointestinal involvement	5	15.2	5	15.2	10	15.2	0.633
Joint involvement	20	60.6	20	60.6	40	60.6	0.599
Vascular involvement	7	21.2	11	33.3	18	27.3	0.204

*Chi-square test

Table 3. Correlations between frequency of flares, BMI, and dietary histamine intake

	BMI (kg/m^2)	
	r*	p*
Frequency of flares	-0.020	0.872
	Dietary histamine intake	
	r*	p*
	0.324	**0.008**

*Spearman's rho correlation analysis. Significant p values are shown in bold.
BMI: Body mass index

inflammatory conditions like Behçet syndrome (16). Although the current study revealed an increase in the frequency of flares with higher BMI, no significant correlation was observed between BMI and the frequency of flares. Koca et al. (17) reported that patients with rheumatism and obesity exhibit greater disease activity than their non-obese counterparts. However, because we did not monitor longitudinal disease activity, other potential correlations may have been missed. Another significant factor contributing to the absence of statistical significance in observed differences could be the prevalence of participants within the ideal BMI range. Patients outside this range were excluded. Nonetheless, it can be inferred that patients with Behçet syndrome would benefit from achieving and maintaining an ideal weight and BMI to mitigate the frequency of flares.

Dietary factors have been implicated in intensifying Behçet syndrome, particularly mucocutaneous lesions (18,19). Some studies have identified specific foods, including vegetables and fruits (such as eggplant, tomatoes, melon, figs, kiwi, and bananas), nuts (walnuts, peanuts, almonds, sunflower seeds), spices (such as pepper), and carbonated beverages, as exacerbating symptoms like oral aphthae, genital ulcers,

Table 4. Correlations between biochemical results and dietary histamine intake

	Dietary histamine intake	
Biochemical results	**r***	**p***
CRP (mg/dL)	-0.336	0.600
ESR (mm/h)	-0.250	0.334
Hemoglobin (g/dL)	-0.276	0.214
WBC (x10^3/uL)	0.650	**0.050**
Platelet count (x10^3/uL)	-0.018	0.948
MCV (fL)	0.097	0.721
RDW (%)	0.168	0.550
BUN (mg/dL)	-0.027	0.937
ALT (IU/L)	-0.111	0.613
AST (IU/L)	-0.180	0.422
Iron binding capacity (ug/dL)	-0.467	0.174
Ferritin (mL/ng)	-0.87	0.800

*Spearman's rho correlation analysis. Significant p values are shown in bold. CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

mucocutaneous lesions, and ocular inflammation in patients (4,19). Consistent with previous research, our study found that 48.5% of participants reported experiencing worsening symptoms upon consuming certain foods. Our findings align with the existing literature, as citrus fruits, acidic beverages, chocolate, spices, and bananas, particularly eggplant, tomatoes, and nuts, emerged as common triggers for symptom exacerbation. Upon further examination of symptoms triggered by these foods, our findings indicated the simultaneous occurrence of oral and genital ulcers alongside dermatologic lesions, consistent with previously documented results. The histamine content of these foods may explain their association with oral and genital ulcers and dermatologic lesions (20). Nuts may elicit allergic reactions by inducing histamine release (21). Additionally, certain foods with acidic, salty, spicy, and coarse textures can irritate the oral mucosa, potentially leading to oral aphthae (22).

The correlation between dietary histamine intake and clinical diagnosis in patients with Behçet syndrome is unclear. However, two studies have reported that certain foods trigger symptoms, such as oral aphthae, genital ulcers, ocular lesions, and dermatologic lesions, in these patients. It was concluded that many of these products were histamine-rich, including ripened cheeses and fermented alcoholic products (4,7). In the current study, we did not observe a significant difference between groups with low and high dietary histamine intake concerning the prevalence of oral aphthae, genital ulcers, uveitis, dermatologic lesions, gastrointestinal involvement, joint involvement, or vascular involvement. Additionally, there was no significant difference in the frequency of flares between the low and high histamine intake groups. However, we did identify a significant positive correlation between dietary histamine intake and the frequency of flares. Histamine exerts its effects on a diverse array of cells, including smooth muscle cells, neurons, endocrine and exocrine cells, blood cells, and various immune system cells. Given its role in regulating leukocyte maturation and activation, as well as its capacity to induce chronic inflammation, histamine plays a pivotal role in driving the development of inflammatory syndromes (23). Hence, it is reasonable to anticipate an association between histamine intake and the frequency of flares in inflammatory conditions such as Behçet syndrome. Consistent with this notion, managing dietary histamine intake may offer a potential route for syndrome management in Behçet patients. Conversely, factors such as stress, trauma, seasonal variations (e.g., temperature, humidity), menstruation, and other dietary constituents with antioxidant or prooxidant properties also influence the frequency of flares (4).

Biochemical findings of Behçet syndrome may be influenced by histamine intake and release (24,25). However, no studies have compared biochemical findings based on histamine intake levels among patients with Behçet syndrome. In the current study, we observed no significant differences in RDW, hemoglobin, and MCV between groups with low and high histamine intake. However, the WBC count was significantly different between the two groups. Moreover, we identified a positive correlation between dietary histamine intake and WBC. This finding suggests that histamine may be associated with an adverse biochemical profile in Behçet syndrome by augmenting inflammation, as evidenced by the elevated WBC count as an inflammatory marker. Only CRP levels were significantly higher than those of the control group, with higher CRP levels and ESR during the flares (26). Higher CRP levels and ESR are commonly observed in various rheumatic syndromes and may arise because of inflammatory processes leading to heightened oxidative stress (27). However, we did not observe significant differences in CRP and ESR levels between the low and high histamine intake groups. Besides, a previous study reported no significant difference in ferritin, iron-binding capacity, ALT, AST, or BUN levels between patients with Behçet syndrome and the control group (28). We observed no significant differences in ferritin, iron-binding capacity, ALT, AST, and BUN levels between the low and high histamine intake groups. It can be concluded that food consumption may be associated with inflammatory markers. Nevertheless, our findings are not consistent with those of previous studies likely due to the short-term follow-up of the clinical findings.

Study Limitations

There are some limitations in this study. First, the study was conducted online and self-funded due to Coronavirus disease-2019 (COVID-19) pandemic measures, which might have reduced the preciseness of the data. COVID-19 has been related to some changes in chronic diseases (29,30).

Additionally, COVID-19 is associated with laboratory findings that may be mixed with the acute phase response seen in Behçet flares and abnormal conditions reported by patients with COVID-19 (31,32). Second, specific biochemical test results were not available to confirm disease activity. Third, other than the oral aphthae, we did not assess the dermatologic findings using objective methods. Whether a participant was in the active disease period could have been erroneous in some patients.

Conclusions

In summary, our study revealed a correlation between heightened dietary histamine intake and an increased frequency of flares in patients with Behçet syndrome. However, biochemical markers such as CRP and ESR were not associated with histamine intake. Nonetheless, limiting the intake of foods that exacerbate symptoms, particularly eggplant, tomatoes, and acidic foods or beverages, during flares may improve quality of life.

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Ethics

Ethics Committee Approval and Informed Consent: Ethics approval for the study was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2022/06-09, date: 19.10.2021), and all participants provided written informed consent. Since voluntariness was taken as the basis for participation, all the participants signed a voluntary consent form.

Authorship Contributions

Surgical and Medical Practices: H.E., N.E., Concept: H.E., N.E., Design: H.E., N.E., Data Collection or Processing: H.E., N.E., Analysis or Interpretation: H.E., N.E., Literature Search: H.E., N.E., Writing: N.E.

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A rare occurrence of primary hyperparathyroidism with brown tumor in the left maxilla

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ABSTRACT

Brown tumors are rare skeletal manifestations of hyperparathyroidism. It is a form of osteitis fibrosa cystica caused by hyperparathyroidism due to excessive secretion of parathyroid hormone. Then, hypercalcemia results in excessive osteoclastic activity in the bones. Brown tumors are considered a rare complication of hyperparathyroidism, as their reported existence is only about 1.5-4.5%. Herein, we report a rare case of brown tumor arising from the left maxilla due to primary hyperparathyroidism, its challenge in diagnosis with giant cell tumor, and its literature review.

Introduction

A brown tumor is a rare, non-neoplastic, reactive bone lesion resulting from excessive parathyroid hormone (PTH) secretion. Histologically, brown tumors are characterized by masses of giant cells surrounding the fibrovascular stroma, cystic spaces in connective tissue, foci of hemorrhage associated with microfracture, and subsequent release of hemosiderin, which gives them their name (1). One of the difficulties encountered in dealing with brown tumors is that they may mimic giant cell tumors (GCT), yet both are different in management. In our cases, the initial workout diagnosis was a GCT of the left maxilla, which raised suspicion when her routine blood investigation revealed hypercalcemia, and the investigation later showed a raised PTH level.

Case Presentation

A 47-year-old female patient with no known comorbidities was admitted with a 1-month history of left maxillary swelling, redness, and tenderness. She had no episode of arrhythmia because her cardiac workout was normal. There were no

gastrointestinal manifestations or any evidence suggesting nephrolithiasis.

Clinical examination revealed a hard left maxillary swelling of approximately 7x6 cm with central ulceration involving the left hard palate crossing the palatal midline. There was no palpable neck swelling.

Subsequent skull X-rays showed an opacified mass in the left maxillary region up to the temporal region. Computed tomography scan revealed a well-defined heterogeneously enhancing soft tissue mass extending into the left maxillary sinus cavity associated with the destruction of the maxillary sinus floor and the inferior part of the nasal septum.

Hyperparathyroidism came to our attention when her blood test revealed a high calcium level of 3.18 mmol/L. Subsequent investigation of intact PTH (i-PTH) revealed a raised level of 79.43 pmol/L.

However, her renal profile was normal, with a urea level of 6.1 mmol/L and a creatinine level of 74 µmol/L. Her phosphate level was 0.52 mmol/L. Thus, we concluded that our patient had primary hyperparathyroidism.

Unfortunately, her left maxillary lesion caused ulceration and recurrent bleeding. Thus, the patient underwent left maxillectomy. Histopathological examination revealed hypercellular proliferation of plump spindled and fibroblastic cells with aggregates of multinucleated giant cells in the presence of large blood-filled cystic spaces, hemorrhage, abundant hemosiderin deposits, and lymphoplasmacytic infiltrates.

Postoperatively, we performed an ultrasound on the neck, which showed a multinodular goiter with a TIRADS-4 nodule at the isthmus, sized at 1.2x2.5x2.2 cm. We then performed a technetium-99m sestamibi scan, which showed evidence of a functioning adenoma at the superior thyroid lobe. The patient was counseled for total thyroidectomy and superior parathyroidectomy; however, she refused to proceed with the suggested surgical intervention and lost follow-up.

Discussion

Primary hyperparathyroidism is more common in women and African Americans than in men and other racial groups. Most cases (>80%) of primary hyperparathyroidism are asymptomatic and are incidentally detected during routine blood investigations. Bandeira et al. (2) reported in a study of 124 patients at their center that 25% showed severe skeletal involvement and osteitis fibrosa cystica (OFC) and 25% had nephrolithiasis. However, a recent cross-sectional study by Eufrazino et al. (3) found that only 6.1% of patients manifested OFC, whereas 18.2% had nephrolithiasis.

Histologically, the present case showed hypercellular proliferation of spindled and fibroblastic cells, multinucleated giant cells, an area of blood-filled cystic spaces, hemorrhage foci, and abundant hemosiderin deposition. This histological manifestation may also mimic GCT, as it shows aggregates of multinucleated GCTs along with a degree of hemosiderin deposition, and some may exhibit a degree of atypia (4).

Clinical and radiological brown tumors and GCTs are difficult to differentiate as both may exhibit clinically exophytic brownish mass and expansile lytic bone lesions with intralesional trabeculation in radiological findings. GCT may favor its growth toward long bones, whereas brown tumors are more favored toward the pelvis, ribs, clavicles, or extremities (5). Thus, increased calcium and PTH levels remained a hallmark of differentiated brown tumors from GCTs.

In our case, the patient presented with a rare brown tumor in the left maxilla. Oral manifestation of brown tumors is considered rare, and tumors involving the oral cavity may exhibit exophytic growth with a high tendency to bleed. Lajolo et al. (6) described in a systematic review that the mandible was the most affected side of intraoral brown tumors (66.2%), with most cases presenting as single lesions (59.5%). When maxillary involvement is detected, it is important to consider the risk of multiple oral lesions.

Patients with tumors that affect their function or quality of life should undergo surgical treatment. There was less evidence-based discussion regarding whether to proceed with parathyroidectomy first, then tumor regression, or undergo tumor resection along with parathyroidectomy in the same setting. There have been cases reported, such as those by Nabi et al. (7), that reported regression of maxillary brown tumors after total parathyroidectomy. Other cases reported by Oliveira et al. (8) showed a large left orbital cavity and part of a brown nasal tumor measuring 8.1 cm x 6 cm x 5.1 cm that regressed after removal of the parathyroid adenoma.

In our case, tumor progression caused episodes of ulceration, obstructing the maxillary sinuses, and recurrent bleeding, requiring multiple hospital admissions. Thus, we first decided to perform a left maxillectomy to improve her quality of life.

Conclusion

Primary hyperparathyroidism with a brown color remained a challenge in management. Early detection and intervention for primary hyperparathyroidism significantly decreased the incidence of brown tumors. The existence of bone mass associated with hypercalcemia should raise suspicion of hyperparathyroidism.

Ethics

Informed Consent: Consent form was filled out by a participant.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: M.A.M.F., S.R.H.I.M., M.M.Y., M.F.O.

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Correction of midline diastema and severe gingival recession with periodontal surgery and orthodontic treatment: A case report with 20 years of follow-up

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ABSTRACT

This case report describes the 20-year outcomes of multidisciplinary treatment in a patient with severe gingival recession, inadequate attached gingiva, and severe midline diastema. Following phase 1 periodontal treatment, mucogingival surgery was performed to create an adequate gingival area in a systematically healthy 20-year-old female patient, followed by orthodontic treatment 3 months postoperatively. The width of the keratinized gingiva increased, the gingival margin moved coronally, and the formation of a new papilla was successful. After 20 years, clinical improvement has remained steady.

Introduction

Gingival recession (GR) refers to the apical displacement of the gingival margin and exposure of the localized or generalized root surface (1,2). Moreover, GR causes esthetics problems and increases the risk of developing hypersensitivity and root caries (3,4). Mucogingival surgeries are performed to correct gingival position and morphology.

This case report aims to describe the multidisciplinary treatment of a patient with an unesthetic appearance due to severe midline diastema, inadequate keratinization of the gingiva, and GR at the anterior mandibular region, followed over 20 years.

Case Presentation

A 20-year-old healthy women admitted to the Gülhane Military Medical Academy, Center for Dentistry Sciences, Department of Periodontology for cosmetic rehabilitation of the diastema between lower middle incisors and GR. Intraoral examination revealed severe GR, inadequate attached gingiva, aberrant frenulum attachment, prominent midline diastema, chronic gingivitis, and orthodontic problems, such as malalignment of the mandibular incisors, labial proclination, and rotation (Figure 1A). After intraoral examination, the width of the keratinized gingiva (WKG) was recorded as 0. GR records were 3 mm for the right and left lower central incisors at the vestibule site, 1 mm at the mesial site of the right lower central tooth, and 2 mm at the mesial site of the left central tooth. The teeth had no pathologic mobility, and the fremitus test result was negative (5).

After the patient completed phase 1 treatment and provided written informed consent, a free gingival graft was harvested from the palate with the overlying epithelium. A graft of approximately 1.5-2 mm thickness was adapted to the recipient site and fixed to the intact keratinized gingiva using non-absorbable sutures (Figure 1B). Three months after surgery, WKG was 7 mm on the right and 6 mm on the left incisors (Figure 1C). The GR of the right central incisor tooth was 3 mm at the buccal site and 1 mm at the mesial site. The diameter was 3 mm at the buccal region and 2 mm at the mesial region of the left central tooth. As a next step, the patient was advised to undergo orthodontic treatment (5). With the orthodontic treatment, creeping attachment formation was observed, and the attached gingival zone increased significantly (Figure 1D). After a 6-month orthodontic treatment, the WKG was 10 mm for the right central tooth and 9 mm for the left central tooth. A 0.5-mm GR was observed only in the vestibule of the left incisor (Figure 1E). Annual controls were planned for the following years (5).

The clinical periodontal status was measured during the 12-year follow-up. The mean WKG was 10 mm for the left incisor and 9 mm for the right incisor. The diastema between the lower central teeth recurred due to the patient's not coming to follow-up regularly, experiencing a pregnancy period, losing the integrity of the lingual retainer, and extraction of the lower second premolar. Since the patient did not want to undergo orthodontic treatment again, composite restorations were made to provide contact with the mesial surfaces of the lower central teeth to improve the esthetic appearance (Figure 2A). Thus, successful papillary reconstruction was achieved via the following process.

In the 20-year follow-up examination, it was noted that the mean WKG was 9 mm for the left incisor and 8 mm for the right incisor (Figure 2B). In conclusion, the patient was happy with her current condition. Keratinized gingiva was formed after the procedures, and the closed diastema remained stable.

Discussion

Before planning dental recession treatment, understandin the predisposing factors is essential. Orthodontic treatment should be considered in addition to a periodontal treatment for poorly aligned teeth with GR (6). Malhotra et al. (7) found

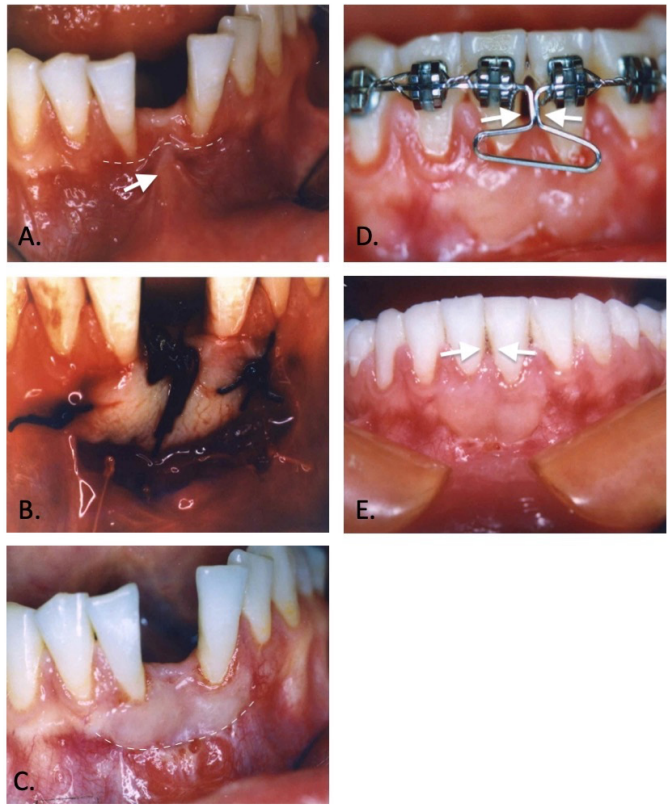

Figure 1. A) Mucogingival problems on the labial aspect of the lower incisors. Note the gingival recession, inadequate keratinized gingiva, and aberrant frenal attachment illustrated by a dashed line. B) Appearance after FGG surgery. C) Appearance of the graft 3 months after the surgery. The appearance of a newly composed keratinized gingiva and a new line of mucogingival junction is illustrated by a dashed line. D) Activation of the "T-loop" to close the midline diastema is illustrated by arrows. E) Reconstruction of periodontal structures following the orthodontic treatment illustrated by arrows (*with permission from Turkish Journal of Medical Sciences)*

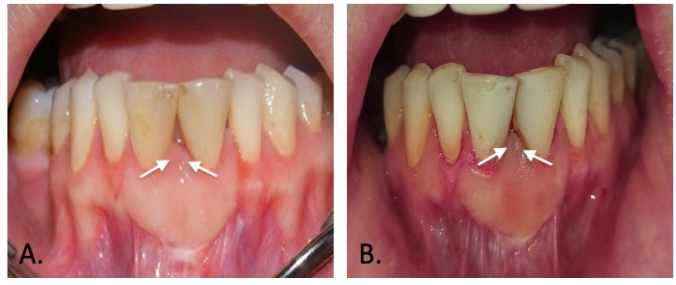

Figure 2. A) Intraoral appearance at 12 years follow-up after composite restorations to make papilla reconstruction since the patient did not want to undergo orthodontic treatment again. B) Intraoral appearance of the reconstructed papilla after 20 years follow-up illustrated by arrows

that an interdisciplinary periodontal-orthodontic approach may be more beneficial in obtaining better primary clinical parameters and esthetics in the treating malaligned mandibular anteriors. Similarly, in the present case, it was observed that clinical parameters, such as attached gingival width, improved with orthodontic treatment. As a result of the movement of the incisor teeth in the lingual direction with orthodontic treatment, the gingival edge moved coronally, resulting in the formation of a new papilla (5). In addition, the examination performed 20 years later revealed that the formation of papillae, which fill the interdental space between the incisors, continued. In a similar 12-year follow-up study, clinical improvement was achieved and successfully maintained with multidisciplinary treatment (8). Other studies have also shown the long-term success of multidisciplinary treatment approaches and soft tissue surgery (9,10).

Diastema loss of the interdental papilla may lead to esthetic and phonetic problems (11). The contact points of the teeth must be provided by proper closure of the diastema for interdental papilla reconstruction without periodontal defects (12). In our case, papilla reconstruction was achieved via periodontal surgery, followed by orthodontic treatment and reshaping of the contacts using composite restorations. Although the diastema recurred between the lower central teeth due to poor attendance and loss of integrity of the lingual retainer, the reconstructed papilla was still stable. In addition, when teeth are moved to a suitable position during the alveolar process, GR can decrease and be accompanied by bone formation. Orthodontic tooth movement is a stimulating factor in bone apposition. In a study involving dogs, Karring et al. (13) showed that lingual movement of teeth can result in bone augmentation. In this study, improved periodontal status was linked to the movement of teeth.

Conclusion

In this case, the biological and functional issues were resolved, and an esthetic improvement was achieved and maintained for over 20 years.

This case report recommends considering multidisciplinary treatment approaches to improve clinical outcomes. More long-term studies with large patient groups are needed to understand the exact mechanism of clinical improvement in the soft and hard tissue components of the periodontium.

Ethics

Informed Consent: Consent form was filled out by a participant.

Authorship Contributions

Surgical and Medical Practices: I.S., Ş.K., Concept: I.S., Ş.K., Design: I.S., Ş.K., Data Collection or Processing: M.Ö.S., V.U.B., Analysis or Interpretation: M.Ö.S., V.U.B., Literature Search: V.U.B., Ö.Ş.G., Writing: I.S., Ö.Ş.G., M.Ö.S.

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Severe orolingual angioedema leading to intubation after tenecteplase administration

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Keywords: Orolingual angioedema, tenecteplase, intravenous thrombolysis, acute ischemic stroke

ABSTRACT

We present the case of a 67-year-old patient who was admitted for a cardiac procedure. Postprocedure the patient experienced hyperacute-onset language deficits. After ruling out contraindications and discussing the risks and benefits, intravenous tenecteplase (TNK) was administered for suspected acute ischemic stroke. Subsequently, the patient developed severe orolingual edema leading to intubation. The patient's condition improved with daily steroids, histamine 2 receptor blocking agents, and antihistamine medications, and she was ultimately discharged home in a stable condition. It is important to remember the possible side effects of intravenous thrombolysis treatment, as timely diagnosis and management can significantly impact the overall prognosis.

Introduction

Intravenous thrombolysis (IVT) is commonly used to treat acute ischemic stroke (1). However, the use of IVT is not without side effects, and the most common side effect is hemorrhagic conversion from ischemic stroke (2). Angioedema is another complication that can lead to life-threatening consequences (3). Tissue plasminogen activator (TPA) has been used as a thrombolytic agent; but in recent years, tenecteplase (TNK) has also become widely used worldwide. We present a case of life-threatening orolingual angioedema leading to intubation after TNK administration for suspected acute ischemic stroke. The patient's clinical status improved with medical management.

Case Presentation

This is a case of a woman patient in her 60s who experienced severe tongue swelling leading to airway compromise and difficulty breathing and swallowing after TNK administration. She initially presented to the hospital for elective transcatheter aortic valve replacement for severe, low-grade aortic stenosis under monitored anesthesia care. After the procedure, she developed

word-finding difficulty with agitation and unequal pupils, leading to a code stroke. Her National Institutes of Health Stroke Scale score at bedside was 3, and it was notable for orientation only to self and language deficits, which are word-finding difficulties known as anomic aphasia. A head computed tomography (CT) scan showed no hemorrhage, and CT angiography ruled out large vessel occlusion. After discussing the risks and benefits, TNK was administered for a suspected acute ischemic stroke. Within 30 min after medication administration, the patient experienced tongue swelling and had difficulty breathing and swallowing. The initial physical examination revealed a firm tongue and floor of the mouth, with the tongue pushing posteriorly. The soft palate was still visible, but the uvula was not. The tongue appeared ecchymotic and congested. Due to rapid swelling and vascular congestion of the tongue, the patient was intubated to prevent airway compromise. During this time, her vital signs remained stable, with appropriate levels of oxygen saturation (Figure 1).

Additional examination revealed hematomas with oozing at the femoral artery puncture sites and left groin. The patient was started on 10 mg oral dexamethasone thrice daily and 20 mg famotidine twice daily. She also underwent bilateral decompressive aspiration of blood from the tongue due to concerns for hematoma, although only 1-2 mL of blood was aspirated. The patient's hemoglobin level fell to 5.3 g/dL on the same day, and she received 1 unit of packed red blood cells, with a follow-up hemoglobin measurement of 7.3 g/dL. Additionally, intravenous 50 mg diphenhydramine once daily was added to her treatment. At this point, her tongue became softer with reduced swelling and could fit inside the patient's mouth. In the following days, tongue size continued to decrease and tongue color became darker until it eventually reached nearly normal size and turgor. Her magnetic resonance imaging of the brain revealed any findings concerning ischemic changes. Following TNK administration, the patient was extubated on day 3, and her tongue returned to nearly its baseline size, as shown in Figure 2, approximately after 5 days. Of note, the patient did not have a history of allergic reactions to medications or latex.

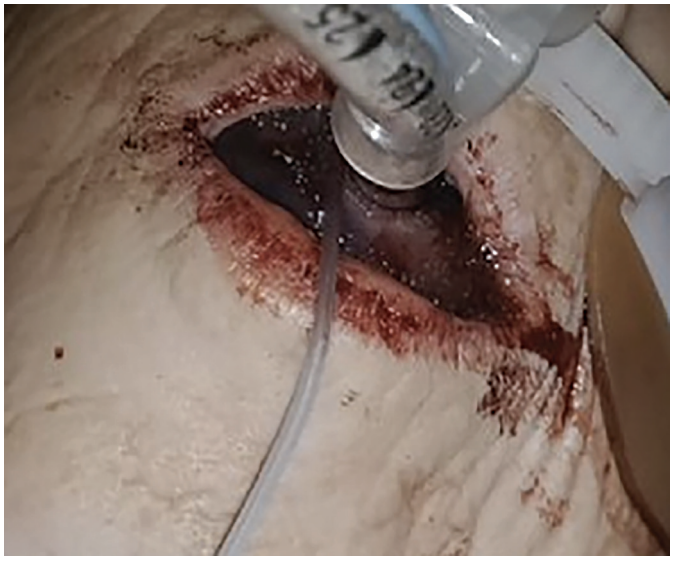

Figure 1. Severe swollen, congested, and ecchymotic tongue after tenecteplase administration

Discussion

IVT is a widely used treatment for patients with suspected acute ischemic stroke, and it has inclusion and exclusion criteria that help identify the most appropriate patients for this treatment. TNK has taken the place of TPA as the drug of choice in most institutions worldwide in the last year. TNK and TPA were reported to be equally effective, and TNK was found to be more affordable (4). The mechanism of action of TNK is related to the hydrolysis of plasminogen into plasmin, leading to the formation of bradykinin. Bradykinin causes vasodilation and increases vascular permeability, which causes the switching of intracellular fluid into interstitial spaces, resulting in angioedema (5). Orolingual angioedema can lead to life-threatening complications due to airway compromise and occurs in around 1-5% of patients receiving IVT for suspected acute ischemic stroke (6). Angioedema may occur during and after IVT treatment, frequently within 25 to 120 minutes after IVT initiation (7). It is important to remember to re-assess patients for signs and symptoms of IVT complications. Prior studies have reported that orolingual angioedema in patients after IVT was localized to the contralateral side of ischemic changes in the brain and was mostly seen in patients with insular cortex involvement due to autonomic dysregulation (7,8). Myslimi et al. (8) reported that 2.2% of patients developed orolingual angioedema, and those

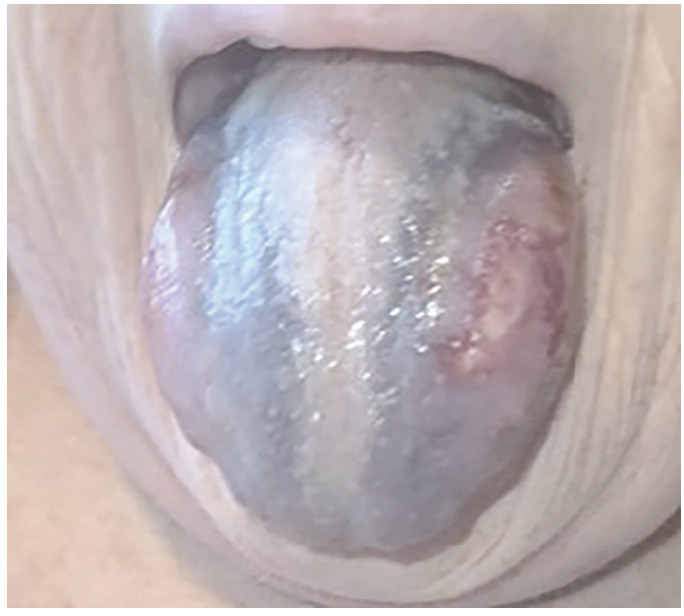

Figure 2. Tongue after the clinical management of severe angioedema and extubation

on angiotensin-converting enzyme-1 agents were most likely to develop this complication. It is worth noting that our patient was not on these agents. This complication did not affect long-term prognosis and modified the Rankin scale if detected and addressed promptly (9). The standard treatment for angioedema mostly includes steroids, epinephrine antihistamines, and H2 blockers (3). In severe cases, the administration of a bradykinin B2 receptor antagonist, a recombinant of kallikrein-inhibiting protein, or fresh frozen plasma may be needed (8).

In this case report, the patient developed severe orolingual angioedema, leading to intubation due to airway compromise after receiving TNK. As reported by Shi et al. (10), in many similar cases, tongue swelling appeared on the ipsilateral side of the vascular injury. However, our patient did not present with imaging findings consistent with a vascular event and developed an allergic reaction. Pitts et al. (11) reported that there is no standardized algorithm highlighting the approach to TNK-related orolingual edema. She was treated with antihistamines, steroids, and H2-blocking agents and experienced clinical improvement without the need for medications previously reported to be used in severe cases. She was extubated successfully and discharged home.

Conclusion

IVT agents are widely used to treat suspected acute ischemic stroke in patients meeting the inclusion and exclusion criteria. Due to its mechanism of action, IVT may lead to angioedema, which is a known complication. In some cases, angioedema may be life-threatening due to impairment of life-sustaining functions, such as airway compromise and respiratory distress, in patients with orolingual edema. The standard management of angioedema includes antihistamines, H2 blocking agents, steroids, and epinephrine. As in our case, emergent intubation may be required in severe cases. This case highlights the importance of close monitoring of patients undergoing IVT for the early recognition of complications. Timely management is the main approach to prevent fatal complications.

Ethics

Informed Consent: Consent for publication was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: H.A-H., U.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Unraveling the complex relationship: Exploring depression's impact on restless legs syndrome

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Keywords: Restless leg syndrome, depression, gastrointestinal symptoms, quality of life

Dear Editor,

The relationship between mental health and physical well-being has long been recognized, prompting increased research into this intricate relationship. Of particular interest is the correlation between depression and neurological disorders, notably restless legs syndrome (RLS). In a recent article published in Gülhane Medical Journal by Çoban et al. (1), the authors shed light on how depression influences RLS, affecting fatigue, quality of life (QoL), and gastrointestinal symptoms. Beginning with an explanation of RLS symptoms and diagnosis, the article underscores the comprehensive impact of the condition, extending beyond mere physical discomfort to encompass ramifications for mental health. Moreover, the authors highlighted studies revealing a heightened prevalence of depression among RLS patients, prompting readers to delve deeper into this significant association (2).

However, a critical lens reveals certain gaps in the study approach. Although the article admirably elucidates the adverse impact of depression on various facets of RLS, it fails to provide a nuanced exploration of the potential causative factors underlying this relationship. For instance, while acknowledging the bidirectional interaction between the brain and gastrointestinal tract, the mechanism merely touches upon the brain-gut axis without delving into the underlying mechanisms. A more robust discussion on the physiological underpinnings of this connection would enrich the discourse. Furthermore, the study's methodology warrants further scrutiny. Although the exclusion of patients on antidepressant medications is understandable, it inadvertently limits the generalizability of findings (3). By homing in on a specific subset of patients with RLS, the study overlooks the broader spectrum of individuals grappling with comorbid depression and RLS. Consequently, the findings may not fully capture the complex interplay between depression and RLS in real-world settings. Moreover, the study's sample size raises concerns about statistical power and generalizability. With a modest cohort of 19 patients, the findings can be regarded preliminary rather than definitive. A larger, more diverse sample would have bolstered the robustness of the findings and lent greater credence to the study's conclusions (4).

Despite these limitations, the study offers valuable insights into the holistic management of RLS, advocating for a comprehensive approach that encompasses mental and physical well-being. By highlighting the detrimental impact of depression on fatigue, QoL, and gastrointestinal symptoms in patients with RLS, the study underscores the importance of addressing mental health concerns alongside conventional treatment approaches. In summary, although the article admirably delves into the connection between depression

and RLS, it could benefit from a deeper examinations of the reasons behind this link and some improvements in its research methods. Taking a critical approach in future studies could help to untangle the complex relationship between mental and physical health in patients with RLS, leading to better treatments and outcomes for those affected.

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Reply to: Unraveling the complex relationship: Exploring depression's impact on restless legs syndrome

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Keywords: Restless legs syndrome, depression, gastrointestinal problems

Dear Editor,

Thank you for your interest in our article. We read your letter with great excitement. As you mentioned, numerous studies have shown (1,2) that people with restless legs syndrome (RLS) also have a variety of comorbidities, particularly psychiatric comorbidities, in addition to the set of symptoms that was needed to diagnose RLS which highlights the importance of comprehensive perspective. This study specifically addressed depression while focusing on fatigue, quality of life, and the gastrointestinal system. This inevitably necessitated a certain amount of mention and focus on each parameter. For example, a discussion of gastrointestinal symptoms was complemented by a mention of the basic mechanism. One of our most important aims with this study is to offer ideas to other researchers for in-depth studies. We think many studies will be performed after this study that examine each parameter separately and devote more space to the mechanisms in line with the author's suggestion. In addition, studies involving physicians specialized in gastrointestinal symptoms may be useful for examining such mechanisms in more detail in future studies. Therefore, we think our study also emphasizes the necessity of multidisciplinary studies. As you mentioned, it is perfectly understandable that we exclude the use of antidepressants. Beyond the fact that antidepressants can have quite adverse effects on the gastrointestinal system (3), it would be extremely biased to include antidepressant-using individuals in our depression-focused study. We agree with your criticism regarding the sample size, but we have also stated this as a major limitation. Analyses in subgroups such as patients using antidepressant were not possible due to the small sample size. However, future studies might be performed with RLS patients receiving antidepressant treatment. Thank you for writing this letter, which gave us the opportunity to clearly reiterate what we recommend for future studies as a result of our study.

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