e-ISSN: 2149-3189

European Research Journal

Volume 10 Issue 6 November 2024

Available at https://dergipark.org.tr/en/pub/eurj

The European Research Journal

Aim and Scope

The European Research Journal (EuRJ) is an international, independent, double-blind peer reviewed, Open Access and online publishing journal, which aims to publish papers on all the related areas of basic and clinical medicine.

Editorial Board of the European Research Journal complies with the criteria of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), and Committee on Publication Ethics (COPE).

The journal publishes a variety of manuscripts including original research, case reports, invited review articles, technical reports, how-to-do it, interesting images and letters to the editor. The European Research Journal has signed the declaration of the Budapest Open Access Initiative. All articles are detected for similarity or plagiarism. Publication language is English. The journal does not charge any article submission or processing charges.

EuRJ recommends that all of our authors obtain their own ORCID identifier which will be included on their article.

The journal is published bimonthly (January, March, May, July, September, and November).

Abstracting and Indexing

The journal is abstracted and indexed with the following: ULAKBIM TR Index (ULAKBİM TR DİZİN), NLM Catalog (NLM ID: 101685727), Google Scholar (h-index: 12), Index Copernicus (ICV 2022: 100), EMBASE, ProQuest Central, EBSCO Academic Search Ultimate, ROAD, SciLit, MIAR (ICDS 2021: 3.8), J-Gate, SHERPA/RoMEO, BASE, EZB, CrossRef, JournalTOCs, WorldCat, TURK MEDLINE, Turkish Citation Index, EuroPub, OpenAIRE, ResearhGate, SOBIAD, Advanced Science Index, ScienceGate, OUCI, Publons, (Clarivate Web of Science)

Publisher

The European Research Journal (EuRJ)
Prusa Medical Publishing
Konak Mh. Kudret Sk. Şenyurt İş Mrk. Blok No:6 İç kapı no: 3
Nilüfer/Bursa-Turkey
info@prusamp.com

https://dergipark.org.tr/en/pub/eurj
https://www.prusamp.com

e-ISSN: 2149-3189

EDITORIAL BOARD

EDITOR-IN-CHIEF

MANAGING EDITORS

FOUNDING EDITOR

EDITORIAL ASSISTANT

EDITORS

Mahmut KALEM, MD,
Associate Professor,
Ankara University Medical School,
Department of Orthopedics and Traumatology,
Ankara, Turkey

Meliha KASAPOGLU AKSOY, MD
Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital,
Department of Physical Therapy and Rehabilitation,
Bursa, Turkey

Burcu DİNÇGEZ, MD
Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital,
Department of Gynecology and Obstetrics,
Bursa, Turkey

Arda ISIK, MD
Associate Professor,
Medeniyet University School of Medicine,
Department of General Surgery,
Istanbul, Turkey

Melih CEKINMEZ, MD
Professor,
University of Health Sciences, Adana City Training & Research Hospital,
Department of Neurosurgery,
Adana, Turkey

Kadir Kaan OZSIN, MD
Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital,
Department of Cardiovascular Surgery,
Bursa, Turkey

Alper KARAKUS, MD
Associate Professor,
University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital,
Department of Cardiology,
Bursa, Turkey

Onur KAYGUSUZ, MD.,
Associate Professor,
Uludag University School of Medicine,
Department of Urology,
Bursa, Turkey

Sayad KOCAHAN, PhD,
Professor,
University of Health Sciences, Gülhane Medical Faculty,
Department of Physiology,
Ankara, Turkey

INTERNATIONAL EDITORIAL BOARD MEMBERS

Table of Contents

Original Articles

Immunosuppressive medication adherence and affecting factors in solid organ transplantation patients: a mixed-methods study 550-560
Emine Selda GÜNDÜZ, Nihal KİRAZ, Aycan KÜÇÜKKAYA, Polat GÖKTAS

Serum oxidative markers and delta neutrophil index in hyperemesis gravidarum 561-567
Gamze YILMAZ, Deniz OLUKLU, Dilek ŞAHİN, Salim NEŞELİOĞLU, Gamze GÖK, Özcan EREL, Hatice AKKAYA, Ayşe Seval ÖZGÜ ERDİNÇ

Retrospective evaluation of functional results and cost analysis of two different anesthesia methods in carpal tunnel syndrome surgery 568-574
Bilal AYKAÇ

A bibliometric analysis of studies conducted over the last 10 years on cardiovascular disease risk identification and prevention in primary care 575-587
Ayşe DAĞISTAN AKGÖZ

Rheumatology nurses' knowledge and practices on pain management 588-599
Seda PEHLİVAN, Serap ÖZER

The economic impact of two-stage knee arthroplasty revisions: a projection for a specialized health center in Türkiye 600-608
Alparslan YURTBAY, Ahmet ERSOY, Cahit Şemsi ŞAY, Ferhat SAY

Comparison of plate and compression screw in the treatment of hallux rigidus with arthrodesis: a retrospective study 609-616
Ahmet YURTERİ, Numan MERCAN, Ahmet YILDIRIM

RETRACTED - Cell transcription dependent on Wingless-type (Wnt)/beta-catenin in the rat estrous cycle stages 617-625
Tuğba DAĞDEVİREN

Review

The significance of personalized medicine in healthcare services of the 21st century: a brief literature review 626-633
Ebru UĞRAŞ TİRYAKİ

Exploring the role of serum sestrin 2 in patients with endometrial polyps and uterine leiomyomas: implications for early diagnosis and pathophysiology 634-643
Selim AKKAYA, Teymur BORNAUN, Hamit Zafer GÜVEN

Case Report

An earthquake reality: fasciotomy wounds and treatments 644-651
Hakan ERDOĞAN, Arzu OTO, Gamze YERCİ, Gülcan KOÇER, Burcu MENEKŞE, Berna AKTÜRK, Ümit YILDIRIM, Şefika Elmas BOZDEMİR

The European Research Journal 2024;10(6):550-560 Original Article

DOI: https://doi.org/10.18621/eurj.1541361 *Transplantation*

Immunosuppressive medication adherence and affecting factors in solid organ transplantation patients: a mixed-methods study

Emine Selda Gündüz[1], Nihal Kiraz[2], Aycan Küçükkaya[3], Polat Göktaş[4]

[1]Department of Medical Services and Techniques, Vocational School of Health Services, Akdeniz University, Antalya, Türkiye; [2]Organ Transplant Clinic, Akdeniz University, Antalya, Türkiye; [3]Department of Hematology Inpatient Service, Koç University Hospital, Istanbul, Türkiye; [4]UCD School of Computer Science, University College Dublin, Belfield, Dublin, Ireland

ABSTRACT

Objectives: Transplantation is a form of treatment that requires long-term pharmacotherapy. After transplantation, patients may have difficulty adapting to medication use for various reasons, and this may result in rejection. The aim of this study is to determine participants' medication compliance and the factors affecting it.

Methods: The research was conducted with a sequential explanatory mixed method. In the study, quantitative data were collected using the Turkish Immunosuppressive Medication Adherence Scale, and qualitative data were collected using the In-Depth Individual Interview Guide. Quantitative data were analyzed using statistical methods, and qualitative data were examined according to Braun and Clarke's thematic analysis framework.

Results: In this study, 62.3% of the participants were male, 37.0% were 50 years old and over, 71.3% lived with their spouse, 54.0% had primary and secondary school education, and 42.0% could not work due to their current health condition. From a clinical perspective, it was determined that 78% of the transplants were kidney transplants, and 41.3% were more than 4 years after transplantation. 74.3% of the transplants were from living donors. The mean score of the immunosuppressive medication compliance scale was determined to be 40.91±4.09. In the qualitative data analysis of the study, factors affecting medication adherence were examined and the themes of "individual factors", "complexity of the regimen" and "social support resources" were obtained. The sub-themes of the individual factors theme are reluctance, hopelessness and addiction; Sub-themes of the complexity of the regimen theme are drug side effects and polypharmacy; The sub-themes of the social support resources theme are loneliness and family pressure.

Conclusions: The factors influencing medication adherence among organ transplant recipients have been investigated, revealing that adherence levels vary significantly depending on various factors. These findings underscore the importance of tailored care strategies and individualized support approaches.

Keywords: Transplantation, medication adherence, nursing, mixed-methods study

Advances in surgical technique and perioperative care have gradually improved the outcomes of solid organ transplantation [1]. However, despite advances in short-term outcomes, long-term graft loss remains a significant problem [2]. Graft rejection is one of the main causes of graft loss

Corresponding author: Emine Selda Gündüz, Lecturer, PhD., RN
Phone: +90 242 227 45 37, E-mail: seldagunduz@akdeniz.edu.tr

How to cite this article: Gündüz ES, Kiraz N, Küçükkaya A, Göktaş P. Immunosuppressive medication adherence and affecting factors in solid organ transplantation patients: a mixed-methods study. Eur Res J. 2024;10(6):550-560. doi: 10.18621/eurj.1541361

Received: August 31, 2024
Accepted: September 30, 2024
Published Online: October 7, 2024

after transplantation; Therefore, understanding the factors that influence graft rejection is important to promote graft survival [3]. Additionally, rejection and the resulting increased burden of immunosuppression increase hospitalization rates, health care costs, and the risk of death from cardiovascular disease and cancer [4].

Immunosuppressive medications are still considered a critical component in the post-transplant care of patients [5]. Immunosuppressive drugs are critical to improve survival and quality of life of post-transplant patients [6]. Regular use of immunosuppressants has a crucial role in minimizing graft loss and maximizing health outcomes in solid organ transplant recipients; However, drug regimens are complex and difficult [7]. One of the most important and often underestimated modifiable factors that strongly influences graft fate is drug nonadherence [8]. Incompatibility is one of the three main causes of post-transplant organ failure, along with organ rejection and infection [9]. Treatment compliance is defined by the World Health Organization (WHO) as "the extent to which the patient's behavior matches clinical prescriptions" [10]. The fact that solid organ transplant patients have to use many medications for many years may cause patients to have difficulties in adapting to medication use [11]. The prevalence of discordance in solid organ transplant recipients is estimated to be between 15% and 30% (5). Non-adherence of patients to medication tends to increase as time passes after transplantation [12].

Knowing the reasons for medication noncompliance is important to increase adherence to medication therapy. A qualitative study reported that participants were nonadherent due to unintentional reasons such as forgetfulness, interference with lifestyle, being asleep at the time the medication was supposed to be taken, change in routine, and the impact of side effects [13]. There are many direct and indirect methods to determine medication non-compliance. Direct methods; directly observed therapy, drug administration visibly supervised by healthcare professionals or caregivers, swallowable sensor system embedded in pills, wireless observed therapy, therapeutic drug monitoring in which differences between expected and observed drug blood levels are investigated, indirect methods; Tracking pill counts, electronic monitoring, and self-report surveys are recommended [4].

In this context, it is important to determine immunosuppressive medication adherence and affecting factors in patients undergoing solid organ transplantation and to develop and implement effective strategies to increase medication adherence of patients after transplantation. Therefore, this study aims to determine medication adherence rates and factors affecting adherence in solid organ transplant patients in Turkey. The results of this study may help improve the health and quality of life of post-transplant patients by contributing to the planning and implementation of nursing interventions to reduce nonadherence.

METHODS

Research Type

This research is an explanatory sequential mixed methods research in which quantitative and qualitative research methods are used together and sequentially to determine immunosuppressive medication adherence and affecting factors in patients undergoing solid organ transplantation. In the first stage of the research, quantitative data was collected. After the analysis of the quantitative data was completed, qualitative interviews were conducted with patients with low scale scores.

Research Place and Time

The research sample consisted of patients who applied to the Akdeniz University organ transplantation clinic between May and November 2022 and met the admission criteria.

Research Population and Sample

Since the number of patients who applied to the outpatient clinic and met the inclusion criteria for the study was not known, the number of samples was calculated as at least 289 for a precision rate of 0.05 and a prevalence of 25% (95% confidence interval) with the formula used for prevalence research when the population was unknown [14]. The sample group was selected by the purposeful sampling method. Patients who had solid organ transplantation at least two months ago and were using immunosuppressive drugs, who could self-administer their medications, who were literate, who were 18 years of age or older, who had no communication problems, and who agreed to participate in the study were included in the study [11].

In the quantitative dimension of the research, the sample consisted of 300 patients and qualitative interviews were conducted with 11 of these patients with low *Turkish Immunosuppressive Medication Adherence Scale* scores. Although it is stated that qualitative research requires five to 25 participants [15] and a small sample group is generally selected [16], it is also stated that terminating the sample is a criterion when the data begins to repeat, in other words, when the data reaches saturation [17]. In this research, transcripts were made day by day and data saturation was checked. Since the research data began to repeat, the data collection process was stopped after the 11th patient.

In this study, the consolidated criteria for reporting qualitative research (COREQ) guidelines were followed.

Data Collection Method

Quantitative data of the study were collected using the Introductory Information Form and *Turkish Immunosuppressive Medication Adherence Scale (TIMAS),* and qualitative data were collected using the In-Depth Individual Interview Guide. Participants who applied to the Akdeniz University organ transplant clinic, met the inclusion criteria, and agreed to participate were informed about the study and gave their written consent. Participants were given the scales and instructed to complete them completely. They were also informed that they would be contacted for an individual interview and their contact information was collected. Due to the nature of the explanatory sequential mixed methods research, quantitative data were collected and analyzed first. Participants with the lowest TIMAS scores were then contacted and invited for qualitative interviews. Individual face-to-face interviews were conducted in a private room in the clinic at a time and date selected by the participants. All in-depth interviews were conducted by the same female researcher (PhD) and lasted between 20 and 40 minutes. With the patients' consent, both recording and note-taking techniques were used during the interviews.

Data Collection Tools

Introductory Information Form

This form was prepared by the researchers and consists of a total of 14 questions about organ transplantation, as well as demographic data such as the participants' age, gender, and education level.

Turkish Immunosuppressive Medication Adherence Scale

This scale, developed by Özdemir, Talas and Öztuna in 2015, consists of a total of 11 items and a single dimension. 5-point and 2-point Likert type rating is used in the scale scoring. 8 items in the scale require "never, rarely, sometimes, often, always" answers, and 3 items require "yes-no" answers. The scale includes 2 positive (4, 6) and 9 negative (1, 2, 3, 5, 7, 8, 9, 10, 11) attitude expressions. A 5-point Likert-type rating is used for positive items, from 1 to 5, and for negative items, from 5 to 1. The lowest score from the scale is 11 and the highest score is 55. The sum of the scores of each item in the scale constitutes the total score of the scale. It is interpreted that as the total score from the scale increases, adherence with medication use increases. The Cronbach alpha coefficient of the scale was calculated as 0.611 [11]. In this study, cronbach's alpha was found to be 0.60.

In-Depth Individual Interview Guide

The interview guide, developed by the researchers, consists of four questions designed to explore how participants define medication non-adherence and their perspectives on the factors influencing it.

Ethical Consideration

Ethics committee approvals were obtained from the Akdeniz University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 530 and date: 25.07.2018) and permission was obtained from the hospital where the research would be conducted. Written informed consent was also obtained from the participants of the study. The Declaration of Helsinki was adhered to throughout.

Statistical Analysis

When assessing immunosuppressant medication adherence and other quantitative data in this study, we used IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) version 28.0 for comprehensive data analysis. It facilitated the thorough examination of both categorical and continuous variables pertinent to our research objectives. Categorical variables such as

gender, marital status, employment status, and type of organ transplanted were summarized using frequency distributions. Continuous variables, including adherence scores, were described using means and standard deviations, providing a quantitative measure of central tendency and variability. The normality of the variables was assessed using the Kolmogorov-Smirnov test and Q-Q plots. To explore relationships and differences within the data, we conducted non-parametric tests, such as Mann-Whitney U and Kruskal-Wallis tests, as appropriate. These analyses were particularly useful in assessing variations across different demographic groups, organ types, and other variables. We ensured the reliability of the TIMAS, by calculating Cronbach's alpha, which provided a measure of internal consistency. A P-value of less than .05 was considered statistically significant in our analyses, aligning with standard practices in research.

Braun and Clark's thematic analysis steps were used to analyze qualitative data. The researchers have received qualitative research training and have qualitative research experience. The audio recordings were transcribed verbatim by the researchers the same day, and participants were asked to check them when available [18].

RESULTS

Quantitative Findings

In this study, 62.3% of the participants were male, 37.0% were 50 years old and over, 71.3% lived with their spouse, 54.0% had primary and secondary school education, and 42.0% could not work due to their current health condition (Table 1).

From a clinical perspective, it was determined that 78% of the transplants were kidney transplants, and 41.3% were more than 4 years after transplantation. 74.3% of the transplants were from living donors, 24.3% from cadavers, and a small portion (1.3%) was from cross-transplantation. When the relationship with the donor was examined, 12.3% was from mothers, 9.0% was from fathers, 15.7% was from siblings, 18.7% was from other relatives, and 20.0% was from unrelated donors (Table 1).

Participants' satisfaction with the surgery outcomes was overwhelmingly positive, with 88.7% reporting being very satisfied. Only a small percentage expressed moderate satisfaction (8.3%) or indecision (2.0%). Regarding post-transplant hospitalizations, 65% of the participants' had been hospitalized post-transplant, while 35% had not. Finally, the majority (97%) reported no difficulties with medication use, whereas a small portion (3%) faced challenges (Table 1).

Table 2 showcased the TIMAS distribution and scoring, shedding light on adherence patterns among this participant group. The descriptive statistics for the adherence to the immunosuppressive medication regimen revealed significant insights into the participants' adherence behaviours. The results indicated a generally high level of adherence, with some areas of concern that merit attention, as provided in the below:

A majority of the participants' reported a high level of adherence to their immunosuppressive medication regimen. The mean score for forgetting to take medication (S1) was 4.53±0.69, indicating that most participants' rarely forget to take their medication. Similarly, the mean score for stopping medication without consulting a doctor (S2) was 4.95±0.32, suggesting that participants' overwhelmingly adhere to their prescribed regimen (Table 2).

The influence of daily activities like school or work (S3) on medication adherence had a mean score of 4.74±0.53, reflecting that participants' generally do not miss their medication due to these activities. However, a lower mean score of 3.62±1.79 was observed for taking forgotten medication within 2-3 hours (S4), suggesting some delays in medication intake upon remembering (Table 2).

Participants' indicated a high level of vigilance in obtaining new supplies (S5) with a mean score of 4.66±1.04. Adjusting medication times according to meal times (S6) had a mean score of 3.98±1.63, implying moderate adherence to timing adjustments (Table 2).

The burden of taking multiple medications (S8) and the challenge posed by daily usage (S7) were rated highly, with mean scores of 4.93±0.31 and 4.90±0.40, respectively. This indicates that most participants' do not find the number of medications or daily usage challenging (Table 2).

In contrast, the responses to questions regarding the past two weeks' adherence patterns (S9, S10, and S11) reflected lower adherence. Participants' reported lower adherence to prescribed doses (1.28±1.02), skipping doses (1.36±1.14), and taking medication outside

Table 1. Overview of organ transplant patients' demographics, clinical profiles, and post-transplant outcomes

Variables		Median (Q1-Q3; min-max); Frequency (Percentage)
Gender	Female	113 (37.7%)
	Male	187 (62.3%)
Age range	18 – 35 years	94 (31.3%)
	36 – 49 years	95 (31.7%)
	50 years and above	111 (37.0%)
Age in years*		43.5 (32-55; 18-76)
Living arrangement	With spouse	214 (71.3%)
	Alone	86 (28.7%)
Education level	Illiterate	17 (5.7%)
	Primary & middle school	162 (54.0%)
	High school	78 (26.0%)
	University degree	43 (14.3%)
Employment status	Employed	74 (24.7%)
	Retired	100 (33.3%)
	Unable to work due to illness	126 (42.0%)
Transplanted organ	Kidney	234 (78%)
	Liver	66 (22.0%)
Post–diagnosis treatments	Medication therapy	189 (28.8%)
	Haemodialysis	151 (23.0%)
	Peritoneal dialysis	30 (4.57%)
	Underwent transplantation	283 (43.1%)
	Others	3 (0.5%)
Time since transplant	Less than 6 months	61 (20.3)
	7 – 12 months	40 (13.3%)
	13 month – 2 years	31 (10.3%)
	2 – 4 years	44 (14.7%)
	Over 4 years	124 (41.3%)
Donor type	Living donor	223 (74.3%)
	Cadaver	73 (24.3%)
	Cross–transplantation	4 (1.3%)
Donor relationship	Cadaver	73 (24.3%)
	Mother	37 (12.3%)
	Father	27 (9.0%)
	Sibling	47 (15.7%)
	Relative	56 (18.7%)
	Others	60 (20.0%)
Satisfaction with surgery outcome	Very satisfied	266 (88.7%)
	Moderately satisfied	25 (8.3%)
	Undecided	6 (2.0%)
	Not very satisfied	3 (1.0%)
Hospitalization post–transplant	No	105 (35.0%)
	Yes	195 (65.0%)
Difficulties with medication use	No	291 (97 %)
	Yes	9 (3%)

Median (Q1–Q3; min.-max.): The median represents the middle value of the dataset, while the interquartile range, delineated by the first quartile (Q1, 25th percentile) and the third quartile (Q3, 75th percentile), captures the middle 50% of the data, indicating its central spread. 'Minimum' denotes the smallest value recorded within the dataset, whereas 'Maximum' refers to the largest value observed

the usual time (1.96±1.71) (Table 2).

The findings suggest that while participants' generally show a high level of adherence to their immunosuppressive medication, with an overall mean score of 40.91±4.09, there are specific areas, particularly related to timely intake and adherence in the immediate past, where improvement is needed. These insights can inform targeted interventions to enhance medication adherence among organ transplant patients (Table 2).

Furthermore, the detailed examination of TIMAS scores across varied demographic and clinical parameters, as provided in Table 3, reveals key insights into medication adherence behaviours among organ transplant recipients. This comparative analysis, covering 300 participants, showcases the influence of factors such as gender, type of transplanted organ, donor characteristics, and the duration since the transplantation on adherence levels. Our findings suggest that while adherence rates did not significantly differ between genders (with females displaying a mean score of 40.49 and males a slightly higher mean of 41.18, P=0.207), the type of transplanted organ did show variation in adherence, albeit not statistically significant (kidney transplant recipients had a mean score of 40.97 versus liver recipients with a mean of 40.74, P=0.530). This suggests that while there are observable differences in adherence behaviours among these groups, they do not reach a level of statistical significance (Table 3).

Notably, the analysis indicates a nuanced effect of donor type on adherence. Participants receiving organs from living donors, cadaver donors, and cross-trans-

Table 2. Descriptive statistics for adherence to immunosuppressive medication regimen and key adherence-related behaviours among patients (n=300).

Statements	Mean±SD
S1: Do you ever forget to take your immunosuppressive medication?	4.53±0.69
S2: Have you stopped taking your immunosuppressive medication without consulting your doctor when you feel well?	4.95±0.32
S3: Do daily activities (such as school or work) cause you to miss or delay the timing of your immunosuppressive medication?	4.74±0.53
S4: If you forget to take your immunosuppressive medication, do you take it as soon as you remember within 2-3 hours?	3.62±1.79
S5: Do you delay obtaining a new supply when your immunosuppressive medications run out?	4.66±1.04
S6: Do you adjust the times you take your immunosuppressive medication according to your meal times?	3.98±1.63
S7: Does the daily use of immunosuppressive medication pose a challenge for you, leading to missed doses?	4.90±0.40
S8: Does the burden of taking multiple immunosuppressive medications lead to missed doses?	4.93±0.31
S9: In the past two weeks, have you taken less than the prescribed dose of your immunosuppressive medication?	1.28±1.02
S10: In the past two weeks, have you missed or skipped doses of your immunosuppressive medication?	1.36±1.14
S11: In the past two weeks, have you taken your immunosuppressive medication a few hours earlier or later than the usual time?	1.96±1.71

This scale comprises 8 items using a 5-point Likert scale (ranging from "Never" to "Always") and 3 items requiring a binary "Yes-No" response. The scale includes 2 positively worded statements (S4 and S6) and 9 negatively worded statements (S1, S2, S3, S5, S7, S8, S9, S10, S11). For positively worded items, scoring is direct with 1 indicating the lowest level of agreement/adherence and 5 the highest. For negatively worded items, scoring is reversed with 5 indicating the lowest level and 1 the highest. For binary items (S9, S10 and S11), the "Yes" response is scored as 1 and "No" as 5. SD=standard deviation

plantation scenarios had mean adherence scores of 41.07, 40.32, and 43.50, respectively, with a near-significant P-value of 0.092, hinting at a potential trend worth further exploration. Furthermore, the adherence varied across donor relationships, showcasing a range of mean scores from 40.34 (cadaver donors) to 42.82 (father), although this variation did not achieve statistical significance (P=0.193). This diversity in adher-

Table 3. Comparative analysis of immunosuppressive drug adherence across different study groups (n=300)

Variables	Study groups		Median (Q1-Q3)	Mean±SD
Gender	Female (n=113)		41.0 (38.5-43.5)	40.49±3.78
	Male (n=187)		42.0 (39.5-44.5)	41.18±4.27
		Test	*Z*=-1.263	
		P value	0.207	
Transplanted organ	Kidney (n=234)		42.0 (39.5-44.5)	40.97±4.12
	Liver (n=66)		40.5 (38.0-43.0)	40.74±4.02
		Test	*Z*=-0.628	
		P value	0.530	
Donor type	Living donor (n=223)		42.0 (39.5-44.5)	41.07±4.18
	Cadaver (n=73)		40.0 (37.5-42.5)	40.32±3.74
	Cross-transplantation (n=4)		43.5 (39.25-47.75)	43.50±4.51
		Test	x^2=4.763	
		P value	**0.092***	
Donor relationship	Cadaver (n=73)		40.0 (37.5-42.5)	40.34±3.74
	Mother (n=37)		42.0 (39.8-44.25)	41.08±3.85
	Father (n=27)		43.0 (38.5-47.5)	42.82±5.02
	Sibling (n=47)		41.0 (38.0-44.0)	41.11±3.63
	Relative (n=56)		42.0 (39.5-42.5)	40.73±4.32
	Others (n=60)		42.0 (39.5-42.5)	40.68±4.22
		Test	x^2=7.387	
		P value	0.193	
Time since transplant	Less than 6 months (n=61)		40.0 (37.5-42.5)	40.61±3.94
	7-12 months (n=41)		43.0 (39.2-46.8)	42.13±4.58
	13 month-2 years (n=31)		42.0 (39.0-45.0)	40.77±4.47
	2-4 years (n=44)		42.0 (39.2-44.8)	41.36±3.57
	Over 4 years (n=124)		41.0 (38.5-43.5)	40.55±4.06
		Test	x^2 =4.308	
		P value	0.230	

Median (Q1-Q3)=The middle value (median) of the dataset and the range between the first quartile (Q1, 25th percentile) and the third quartile (Q3, 75th percentile), representing the central 50% of the data. Mean±SD=The average value (mean) of the data plus or minus the standard deviation (SD), which describes the spread of the data around the mean. The symbols *(P<0.05) denoted levels of statistical significance for differences or correlations, indicating the likelihood that the observed differences or relationships occurred by chance.

ence rates underscores the complexity of interpersonal relationships and their potential impact on medication adherence (Table 3).

The time elapsed since the transplant also played a role in adherence behaviours, with scores ranging from 40.55 (over 4 years post-transplant) to 42.13 (7-12 months post-transplant), though these differences were not statistically significant (P=0.230). This suggests that the time factor might influence adherence patterns, warranting further investigation to understand its implications fully (Table 3).

In summary, the analysis of the TIMAS scale underscores that while certain factors like gender, organ type, donor characteristics, and post-transplant duration offer insights into adherence behaviours, the statistical significance of these observations varies. These findings emphasize the need for personalized intervention strategies targeting specific demographic and clinical characteristics to enhance medication adherence and ultimately improve outcomes for organ transplant recipients.

Qualitative Findings

In the qualitative data analysis of the study, factors affecting medication adherence were examined and the themes of "individual factors", "complexity of the regimen" and "social support resources" were obtained. Under the theme of individual factors, patients expressed their reluctance, hopelessness and feelings of addiction towards drug use (Table 4).

In the participants' statements, it was determined that they were reluctant to use medication because they were tired of using medication, they were afraid of developing rejection due to repeated hospitalizations and medication side effects, and that they thought rejection would occur one day, and that they thought they were dependent because they were constantly in need of the hospital or someone else. In the theme of regimen complexity, participants reported that medication side effects and polypharmacy negatively affected adherence to medication use. In the theme of social support sources, participants stated that reasons such as loneliness and family pressure negatively affected their adherence to treatment (Table 4).

Tablo 4. Reasons for participants' non-adherence to medication use (n=11)

Main Theme	Sub-theme	Quotations
Individual factors	Reluctance	People get bored sometimes. You have been on dialysis for years, now medication, medication, medication. Sometimes I don't feel like doing anything (P*11).
	Hopelessness	I am in the hospital every month. No matter what I do, there is no peace for me. I'm fed up. What else can I do? (P4)
	Addiction	It's like you can't live your life, you always have to be in control. You're lucky, but sometimes you feel like rebelling (P5).
Complexity of the regimen	Drug side effects	Medications cause insomnia, you feel nauseous, you become disorganized. Sometimes people can't do everything they need to do. (P9).
	Polypharmacy	There are so many drugs. Even though I set a reminder, sometimes I still forget or get confused (P1).
Social support resources	Loneliness	My wife died. What should I ask from whom? That's what I do. My daughter says come to us, but I can't fit in with anyone, I can't take shelter in them (P10).
	Family pressure	Everyone is telling you something. It's like everyone knows better than you. I am tired. I feel like getting angry at them and not taking the medicine secretly. It's like they're constantly watching you. If you make a mistake they get mad at you like a child (P2).

The identities of the participants are stated as P1-11 for anonymity.

DISCUSSION

The descriptive analysis of the TIMAS reveals a generally high adherence level among organ transplant patients, with an overall mean score of 40.91±4.09. Key findings indicate strong adherence to medication schedules, with participants' rarely forgetting to take their medication or stopping it without consulting a doctor. Daily activities like work or school minimally impact medication adherence, underscoring a commitment to their regimen. However, the study highlights areas for improvement, notably in managing the timely intake of missed doses and handling multiple medications. The most significant concerns arise from the lower adherence observed in the past two weeks, particularly in maintaining prescribed doses and adhering to the medication schedule. In a study, the average TIMAS score of the participants was found to be 48.10±6.61 [19]. In another study, a statistically significant negative relationship was reported between TIMAS scores and time after transplantation, according to the results of Pearson correlation analysis. It was found that as the time passed after transplantation increased, the TIMAS scores of the participants decreased [19]. These findings underscore the need for targeted interventions to bolster adherence, especially in addressing short-term lapses. Enhancing patient education and support, particularly in managing complex medication schedules, could significantly improve treatment outcomes for organ transplant recipients. The literature reports that the prevalence of incompatibility in solid organ transplant recipients is between 15% and 30% [5]. A study reported that 16.47% of patients were non-compliant with treatment [20]. There are a limited number of studies reporting the non-compliance rate with immunosuppressive drug use in transplanted patients in Turkey [19]. In our study, it appears that the compliance rate with immunosuppressive drug therapy is low compared to other results [11, 19].

Furthermore, the findings from our analysis of the TIMAS offer valuable insights into the nuanced landscape of medication adherence among organ transplant recipients, as detailed in Table 3. The lack of statistically significant differences in adherence related to gender and the type of transplanted organ suggests that while these factors are important to consider, they may not be the primary determinants of adherence behaviour. However, the observed trends in adherence variations associated with donor type and the time since transplantation, despite not reaching statistical significance, highlight potential areas for targeted interventions. Particularly, the near-significant difference in adherence scores among recipients of organs from living donors, cadaver donors, and through cross-transplantation suggests that the source of the organ might influence participants' adherence to their immunosuppressive medication regimen. Additionally, the variation in adherence across different donor relationships and time intervals since transplantation underscores the complexity of factors influencing adherence. These findings point towards the importance of developing personalized, context-sensitive intervention strategies that address the specific needs and circumstances of individual participants'. Although existing literature has cited interventions such as support tools (e.g., reminder systems), monitoring strategies, and continuing education to improve adherence, studies have largely fallen short of providing conclusive evidence of their effectiveness [21]. By focusing on the multifaceted nature of medication adherence, healthcare providers can better support organ transplant recipients in achieving optimal outcomes through improved adherence to their prescribed medication regimens.

It has been reported that compliance can be affected by a wide variety of factors, both personal and environmental, and that the characteristics of the disease or regimen can also affect adherence [22]. In the qualitative data analysis of the research, the themes of individual factors, complexity of the regime and social support sources were obtained. Under the theme of individual factors, patients expressed their reluctance to use medication, their hopelessness, and their feelings of dependence on medication. Research suggests that having strong beliefs that a medication is needed does not necessarily lead to adherence to treatment unless combined with low concerns about taking the medication [23].

In the theme of Regimen Complexity, participants reported that medication side effects and polypharmacy negatively affected adherence to medication use. Having a disease that requires regular use of more than one medication is an important factor that makes medication compliance difficult for individuals [24]. Similarly, other studies have reported that polypharmacy negatively affects medication adherence [25, 26].

Regarding the theme of social support sources, participants stated that reasons such as loneliness and family pressure negatively affected their adherence to treatment. There is evidence that social support is associated with increased likelihood of engagement, particularly regarding the quality of support rather than the presence of other people [22]. One study reported that determinants of post-transplant medication adherence were medication-related factors such as inappropriate dosing, insufficient medication knowledge difficulty in remembering medication dosage and timing, and economic constraints in continuing medical treatment [20].

Limitations

This study reflects single center findings. Qualitative findings cannot be generalized due to their nature. Furthermore, just one of the researchers conducted the face-to-face interviews, which could have resulted in an unexpected social bias.

CONCLUSION

This study's detailed examination of the TIMAS offers crucial insights into the medication adherence behaviours of post-solid organ transplant patients. Contrary to initial expectations, the results suggest that adherence levels, while generally high, exhibit significant variability influenced by factors such as gender, type of transplanted organ, donor characteristics, and the duration since the transplant. This variability highlights the intricate dynamics of medication adherence within the post-transplant environment, stressing the need for customized care strategies. The study particularly illuminates the nuanced challenges that transplant recipients face, including the management of complex medication regimens and the adaptation of their daily routines to accommodate these schedules. Noteworthy are the observed adherence disparities across different demographic and clinical subgroups, pinpointing the necessity for individualized education and support strategies. These are especially critical for those newly post-transplant or those facing unique personal challenges.

In light of these findings, there is a clear directive for the development of targeted interventions and enhanced support mechanisms aimed at improving medication adherence for organ transplant recipients. Healthcare professionals are provided with a foundation to refine patient counselling approaches, tackle specific adherence obstacles, and ultimately, uplift the quality of life and clinical outcomes for this patient group. Future investigations should seek to overcome the current study's limitations by broadening the participant base and employing varied methodological designs. Such efforts are crucial to deepen our comprehension of adherence behaviours and to fine-tune intervention strategies for this essential patient demographic, ensuring they receive the most effective and personalized care possible.

In addition to the results of this study, methods such as reducing pill burden, educational-behavioral intervention, medication reminder intervention, and remote monitoring are among the ways to increase medication compliance in the literature. Because medication nonadherence after solid organ transplantation arises from a diverse set of partly dynamic causes and is predominantly unintentional, simple or general solutions are not available and therapeutic interventions require a persistent, holistic, individualized patient approach and a multidisciplinary support team.

Authors' Contribution

Study Conception: ESG, NK, AK, PG; Study Design: ESG, NK, AK, PG; Supervision: ESG, NK, AK, PG; Funding: N/A; Materials: ESG, NK; Data Collection and/or Processing: ESG, NK; Statistical Analysis and/or Data Interpretation: ESG, NK, AK, PG; Literature Review: ESG, NK, AK, PG; Manuscript Preparation: ESG, NK, AK, PG and Critical Review: ESG, NK, AK, PG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Lerut J, Iesari S, Foguenne M, Lai Q. Hepatocellular cancer and recurrence after liver transplantation: what about the impact of immunosuppression? Transl Gastroenterol Hepatol. 2017;2:80.

doi: 10.21037/tgh.2017.09.06.
2. Wojciechowski D, Wiseman A. Long-Term Immunosuppression Management: Opportunities and Uncertainties. Clin J Am Soc Nephrol. 2021;16(8):1264-1271. doi: 10.2215/CJN.15040920.
3. Oweira H, Ramouz A, Ghamarnejad O, et al. Risk Factors of Rejection in Renal Transplant Recipients: A Narrative Review. J Clin Med. 2022;11(5):1392. doi: 10.3390/jcm11051392.
4. Gandolfini I, Palmisano A, Fiaccadori E, Cravedi P, Maggiore U. Detecting, preventing and treating non-adherence to immunosuppression after kidney transplantation. Clin Kidney J. 2022;15(7):1253-1274. doi: 10.1093/ckj/sfac017.
5. Shafiekhani M, Shahabinezhad F, Tavakoli Z, et al. Quality of life associated with immunosuppressant treatment adherence in liver transplant recipients: A cross-sectional study. Front Pharmacol. 2023;14:1051350. doi: 10.3389/fphar.2023.1051350.
6. Malek-Hosseini SA, Habibzadeh F, Nikeghbalian S. Shiraz Organ Transplant Center: The Largest Liver Transplant Center in the World. Transplantation. 2019;103(8):1523-1525. doi: 10.1097/TP.0000000000002581.
7. Tang J, Kerklaan J, Wong G, et al. Perspectives of solid organ transplant recipients on medicine-taking: Systematic review of qualitative studies. Am J Transplant. 2021;21(10):3369-3387. doi: 10.1111/ajt.16613.
8. Wang JH, Skeans MA, Israni AK. Current Status of Kidney Transplant Outcomes: Dying to Survive. Adv Chronic Kidney Dis. 2016;23(5):281-286. doi: 10.1053/j.ackd.2016.07.001.
9. Moradi O, Karimzadeh I, Davani-Davari D, Shafiekhani M, Sagheb MM. Pattern and associated factors of adherence to immunosuppressive medications in kidney transplant recipients at a referral center in Iran. Patient Prefer Adherence. 2019;13:729-738. doi: 10.2147/PPA.S198967.
10. Ahmed R, Aslani P. What is patient adherence? A terminology overview. Int J Clin Pharm. 2014;36(1):4-7. doi: 10.1007/s11096-013-9856-y.
11. Koken ZO, Talas MS, Gokmen D. Development and Psychometric Testing of the Turkish Immunosuppressive Medication Adherence Scale. Turkish J Nephrol. 2019;28(2): 120-126. doi: 10.5152/turkjnephrol.2019.3371.
12. Gokoel SRM, Gombert-Handoko KB, Zwart TC, van der Boog PJM, Moes DJAR, de Fijter JW. Medication non-adherence after kidney transplantation: A critical appraisal and systematic review. Transplant Rev (Orlando). 2020;34(1):100511. doi: 10.1016/j.trre.2019.100511.
13. Muduma G, Shupo FC, Dam S, et al. Patient survey to identify reasons for non-adherence and elicitation of quality of life concepts associated with immunosuppressant therapy in kidney transplant recipients. Patient Prefer Adherence. 2016;10:27-36. doi: 10.2147/PPA.S96086.
14. Lwanga SK, Lemeshow S, World Health Organization. Sample size determination in health studies: a practical manual. World Health Organization, 1991.
15. Joseph ML. Innovativeness ın nursing: a phenomenological and constructivist study. Capella University, Dissertation 2007. http://www.kutuphane.istanbul.edu.tr/everitaban.html
16. Polit DF, Beck CT. Essentials of Nursing Research. 6th Edition, Lippincott William & Wilkins: Philadelphia. 2001.
17. Aksayan S, Bahar Z, Seviğ Ü. Hemşirelikte Araştırma İlke Süreç ve Yöntemleri. İ. Erefe (Ed.), İstanbul: Odak Ofset, 2002.
18. Braun V, Clarke V. What can "thematic analysis" offer health and wellbeing researchers? Int J Qual Stud Health Well-being. 2014;9:26152. doi: 10.3402/qhw.v9.26152.
19. Köken ZÖ, Karahan S, Sezer R E, Abbasoğlu O. [Immunosuppressive Medication Adherence in Liver Transplant Patients: A Single Center Experience]. Ahi Evran Medical Journal. 2020;4(3):88-95. [Article in Turkish]
20. Jain M, Venkataraman J, Reddy MS, Rela M. Determinants of Medication Adherence in Liver Transplant Recipients. J Clin Exp Hepatol. 2019c;9(6):676-683. doi: 10.1016/j.jceh.2019.03.003.
21. Yoon ES, Hur S, Curtis LM, et al. A Multifaceted Intervention to Improve Medication Adherence in Kidney Transplant Recipients: An Exploratory Analysis of the Fidelity of the TAKE IT Trial. JMIR Form Res. 2022;6(5):e27277. doi: 10.2196/27277.
22. Stewart SF, Moon Z, Horne R. Medication nonadherence: health impact, prevalence, correlates and interventions. Psychol Health. 2023;38(6):726-765. doi: 10.1080/08870446.2022.2144923.
23. West LM, Borg Theuma R, Cordina M. The 'Necessity-Concerns Framework' as a means of understanding non-adherence by applying polynomial regression in three chronic conditions. Chronic Illn. 2020;16(4):253-265. doi: 10.1177/1742395318799847.
24. Eriksen CU, Kyriakidis S, Christensen LD, et al. Medication-related experiences of patients with polypharmacy: a systematic review of qualitative studies. BMJ Open. 2020;10(9):e036158. doi: 10.1136/bmjopen-2019-036158.
25. Franchi C, Ludergnani M, Merlino L, et al. Multiple Medication Adherence and Related Outcomes in Community-Dwelling Older People on Chronic Polypharmacy: A Retrospective Cohort Study on Administrative Claims Data. Int J Environ Res Public Health. 2022;19(9):5692. doi: 10.3390/ijerph19095692.
26. Lavrador M, Cabral AC, Castel-Branco M, Figueiredo IV, Fernandez-Llimos F. Polypharmacy and medication adherence. In: Aging. From Fundamental Biology to Societal Impact. Oliveira P, Malva JO. eds., Academic Press. 2023; pp.435-453. doi: 1016/B978-0-12-823761-8.00014-8.

The European Research Journal 2024;10(6):561-567 Original Article

DOI: https://doi.org/10.18621/eurj.1521624 *Obstetrics and Gynecology*

Serum oxidative markers and delta neutrophil index in hyperemesis gravidarum

Gamze Yilmaz[1], Deniz Oluklu[2], Dilek Şahin[2], Salim Neşelioğlu[3], Gamze Gök[3], Özcan Erel[3], Hatice Akkaya[1], Ayşe Seval Özgü-Erdinç[2]

[1]Department of Obstetrics and Gynecology, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye; [2]Department of Perinatology, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye; [3]Department of Medical Biochemistry, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye

ABSTRACT

Objectives: To evaluate the relationship between different serum oxidative markers and the delta neutrophil index and hyperemesis gravidarum.

Methods: One hundred pregnant women were enrolled in the study and divided into two groups. Group 1 included 50 women with hyperemesis gravidarum, while Group 2 (control group) included 50 pregnant women similar in age, gestational week, and body mass index. Serum oxidative markers and complete blood count inflammatory markers were compared.

Results: Native thiol and total thiol were significantly lower in the Group 1 when compared with the control group (P=0.029 for native thiol; P=0.035 for total thiol). Moreover, ischemia-modified albumin (IMA) and catalase values were significantly higher in the Group 1 than in the control group (P=0.023 for IMA; P=0.021 for catalase). Index1% shows the disulfide/native thiol percent ratio and means that the Group 1 oxidant load is increased but not statistically significant. Myeloperoxidase, ferroxidase, and the delta neutrophil index did not differ significantly between the two groups (P=0.591, P=0.793, and P=0.52; respectively).

Conclusions: According to our study, contrary to the literature, although there are differences in some values, when evaluated individually hyperemesis gravidarum does not impose an extra burden on maternal oxidant-antioxidant balance.

Keywords: Oxidative hemostasis, hyperemesis gravidarum, delta neutrophil index

Hyperemesis gravidarum (HG) is an important reason for hospitalization in the early stages of pregnancy and is seen in approximately 0.3-3% of pregnancies. Its definition according to the American College of Obstetricians and Gynecologists (ACOG) guidelines in 2015 is still unclear. Constant nausea and vomiting not associated with other causes, ketonuria, dehydration, electrolyte disturbances, and monitoring of approximately 5% of pre-pregnancy weight loss are frequently determined criteria for the diagnosis of HG [1]. There are different studies in the literature on the etiology of HG, which is not elucidated. Psychological causes, pregnancy hormones, gastritis, and genetic causes were investigated, but the main cause remains unclear [2-5]. One investigated etiology is imbalance between oxidant and antioxi-

Corresponding author: Gamze Yılmaz, MD.,
Phone: +90 312 552 60 00, E-mail: gamze_u@hotmail.com

How to cite this article: Yılmaz G, Oluklu D, Şahin D, et al. Serum oxidative markers and delta neutrophil index in hyperemesis gravidarum. Eur Res J. 2024;10(6):561-567. doi: 10.18621/eurj.1521624

Received: July 25, 2024
Accepted: September 24, 2024
Published Online: October 11, 2024

dants. When healthy pregnancies were examined, it was found that antioxidant activity was higher than in the non-pregnant ones [6]. Many studies have reported that antioxidants decrease in HG and the situation shifts towards oxidants [7].

Oxidative stress (OS) is a condition that causes cellular and molecular damage resulting from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system that buffers oxidative damage. In many pathological conditions associated with pregnancy such as HG, it has been found that antioxidant activity decreases and the balance shifts to the oxidant side [2, 8, 9].

There are oxidant and antioxidant mechanisms in the human body that act against stressors. An enzyme found in the antioxidant defense system is ferroxidase, which converts toxic iron to less toxic ferric iron to reduce cellular and molecular oxidative damage [10, 11]. Another intracellular antioxidant is catalase (CAT). Its main purpose is to neutralize intra- and extracellular hydrogen peroxide, so its level increases in cases of OS [12]. Myeloperoxidase (MPO) is another intracellular enzyme found in neutrophils and is involved in the antioxidant system [13]. Thiols are protective organic components that are specified against ROS [14]. Thiols contain sulfhydryl (SH) groups, which react with oxidant molecules and change as a result of oxidation. Proteins mutate due to the changes in thiol groups, resulting in structural and functional changes [15]. Ischemia-modified albumin is a biochemical marker that increases in some situations such as ischemia, acidosis, or hypoxia. A somewhat hypoxic intrauterine environment occurs in the physiology of pregnancy. Reperfusion and OS that occur afterward are important for trophoblast development. In previous publications, IMA elevation was found in the early pregnancy period [16-18].

The delta neutrophil index (DNI) is a marker showing the number of immature granulocytes in human serum. In a limited number of studies, the DNI was used in patient groups with inflammatory processes [19]. The number of studies investigating whether it is associated with hyperemesis is limited.

To the best of our knowledge, our study is the first to evaluate many more oxidant and antioxidant active parameters in the same patient with a somewhat larger number of patients compared to previous studies. The main aim of our study was to determine the direction of serum oxidation balance in pregnancy nausea and vomiting, to clarify the literature, and to give a clear answer to pregnant women who are very concerned about themselves and their babies during this process.

METHODS

This case-control study was conducted in the Obstetrics and Gynecology clinic of our tertiary hospital between December 2022 and March 2023. One hundred pregnant women who were referred to the Obstetrics Department of our hospital were enrolled. The Ethical Committee of our hospital approved the study protocol (No: E2-22-2647, date: 26.10.2022). Informed consent was obtained from each participant. The diagnostic criteria for HG were determined by the ACOG Practice Bulletin No. 153: nausea and vomiting of pregnancy. All the pregnant women were in the first trimester (≤14 weeks). Fifty patients with a diagnosis of HG who were admitted to the hospital for the first time and had not received any medication for emesis

Table 1. Demographic parameters in HG and control groups

Parameters	Control	HG	P value
Age (years)	27.47±3.81	26.94±5.04	0.560
Gravidity	1.81±0.77	1.96±1.02	0.762
Parity	0.79±0.75	1.12±1.52	0.215
Gestational week	9.74±2.28	10.12±2.25	0.667
BMI (kg/m^2)	25.49±4.99	26.94±4.42	0.265

Data are shown as mean±standard deviation, HG=hyperemesis gravidarum, BMI=body mass index. Independent sample t-test was applied.

Table 2. Levels of serum oxidative markers in HG and control groups

Parameters	HG	Control	P value
Native thiol (µmol/L)	375.35±96.64	414.6±73.14	**0.029***
Total thiol (µmol/L)	416.69±106.34	458.04±79.13	**0.035***
Disulfide (µmol/L)	20.67±7.49	21.72±6.6	0.474
IMA (ABSU)	0.81±0.17	0.72±0.19	**0.023***
Index1 (%)	5.64±2.11	5.28±1.47	0.336
Myeloperoxidase (U/L)	91.08±19.64	93.4±22.55	0.591
Catalase (U/L)	197.19±39.11	180.01±31.71	**0.021***
Ferroxidase (U/L)	448.37±59.5	445.1±62.68	0.793

Data are shown as mean±standard deviation, HG=hyperemesis gravidarum, IMA= ischemia-modified albümin, index1=disulfide/native thiol percent ratio. Independent sample t-test was applied

*P<0.05 was considered significant.

before were compared with 50 pregnant women similar in age, gestational week, and body mass index (BMI). The number of ketones in the urine of all pregnant women in the HG group was the same. Although the pregnant women in both groups did not have any chronic disease, the patient group with HG did not have any additional medical problems other than pregnancy to explain their nausea, vomiting, and weight loss. All participants had intrauterine fetuses with normal heart rates. The maternal age, BMI, parity, gravidity, and gestational weeks of all the pregnant women were recorded.

Fasting blood samples from all volunteers before medication was placed into plain tubes. Sera were separated after centrifugation at 1600 × g for 10 minutes and stored at -80 °C until the time of analysis.

Thiol/disulfide homeostasis tests were performed using an automated spectrophotometric method as described by Erel and Neselioglu [15]. The albumin cobalt binding test was used to detect the presence of IMA [19]. Ceruloplasmin levels were measured by the method described by Erel [21]. This method is automated, colorimetric, and based on the enzymatic oxidation of ferrous ions to ferric ions. Serum MPO activity was measured by a modification of the o-dianisidine method [22]. CAT activity was measured by Goth's method [23].

Statistical Analysis

The statistical analysis was performed using SPSS for Windows 18.0 (IBM, Chicago, IL, USA). The mean and frequency values of the variables were calculated. The Kolmogorov–Smirnov test was used to detect whether the numerical values were normally distributed. Student's t-test was used to compare normally distributed values and the Mann–Whitney U test was used to compare non-normally distributed values. P<0.05 was considered statistically significant.

RESULTS

Table 1 contains the demographic features of the study participants including age, gravidity, parity, gestational week, and BMI. Comparison of the two groups shows that the participants have a similar distribution in terms of demographic features.

Table 2 shows the differences between the two groups in terms of thiol hemostasis, IMA, MPO, CAT, and ferroxidase. The differences between the groups were analyzed. Native thiol, total thiol and catalase levels were lower in the HG group (P=0.029, P=0.035, and P=0.021; respectively) while the level of IMA was higher compered to in the control group.

In Table 3, inflammatory markers in complete blood parameters, especially the DNI, which is associated with the severity of the disease in inflammatory events in recent years, was also compared. No statistically significant difference was found in any of the complete blood parameters between the groups.

Table 3. Complete blood count inflammatory markers in HG and control groups

Variables	HG	Control	P value
Neutrophil count ($\times 10^9$/L)	6.40±2.18	6.57±1.86	0.632
Lymphocyte count ($\times 10^9$/L)	1.91±0.62	2.06±0.58	0.142
Monocyte count ($\times 10^9$/L)	0.44±0.17	0.40±0.11	0.463
Plateletcrit (%)	0.22± 0.05	0.22±0.05	0.889
Platelet distribution width (fL)	51.15±7.21	51.95±7.25	0.615
Platelet count ($\times 10^9$/L)	278.42±74.03	264.46±66.39	0.309
Hemoglobine(g/dL)	12.8±1.21	12.61±1.07	0.173
Neutrophil/lymphocyte ratio	13.51±58.9	3.34±0.99	0.357
Delta neutrophil index (%)	0.32±0.97	0.52±1.81	0.52
Large unstained cell count ($\times 10^9$/L)	0.12±0.54	0.11±0.03	0.30

Data are shown as mean±standard deviation, HG=hyperemesis gravidarum. Mann-whitney u test was applied. *P<0.05 was considered significant.

DISCUSSION

In many studies on oxidants and HG, it has been stated that oxidant and antioxidant balance shifts towards the oxidant side. Contrary to the literature, we believe that HG may not have caused extra oxidative load for the mothers.

In thiol/disulfide balance, native and total thiol levels show antioxidant status while the index1% value shows the balance between oxidants and antioxidants. According to our study, the level of antioxidants in terms of thiol/disulfide was lower in the HG group (P=0.029 and P=0.035, respectively). The literature also supports this situation and studies have found a decrease in total antioxidant activity in HG [6, 8, 24]. In a previous study the balance was shifted to the oxidant side with the decrease in antioxidants in 26 pregnant women with HG [24]. Index1% shows the disulfide/native thiol percent ratio and the oxidative balance. In our study, although there was a decrease in antioxidant activity, it was not statistically significant between the two groups in terms of oxidative balance (index1%, P=0.336). Therefore, in studies conducted with thiol/disulfide balance to date, considering that the number of participants is higher than in previous studies, we can conclude that the oxidative balance does not make a significant difference when HG patients and pregnant women without HG are compared.

IMA is a rapidly increasing biomarker in clinical response conditions such as hypoxia, acidosis, and myocardial ischemia. In previous studies, increased levels of IMA have been reported in complicated pregnancies involving fetal growth retardation, recurrent pregnancy loss, first-trimester miscarriages, and preeclampsia [25-29]. Papageorghiou *et al*. found that serum IMA levels are higher in defective endovascular trophoblast invasion. They argued that the trophoblast may trigger improper development because of the high degree of intrauterine hypoxia and subsequent reperfusion-related oxidative damage [16]. There are also different studies in the literature stating that IMA levels increase physiologically in early gestational weeks [17, 18]. Recently, Uckan *et al*. [30] found high IMA levels in 137 women with pregnancies complicated by HG. Although the level of IMA was significantly higher in our study, it is not clear whether this marker, which was already determined to be high in the first period of pregnancy, increased even more due to HG or its high level played a role in the etiopathogenesis of HG.

MPO is a lysosomal enzyme secreted from leukocytes in response to OS. It was reported that the levels of MPO, which was determined at increased levels in complicated pregnancies like preeclampsia and idiopathic intrauterine growth restriction, did not differ significantly in the three trimesters in healthy pregnancies [31, 32]. There is one study in the literature

conducted on the relationship between HG and MPO in 30 women and the results are consistent with those of our study. They found statistically significant low levels of MPO in HG [33]. However, in our study, although low MPO levels were observed, there was no statistically significant difference compared to control group. This indicates that HG does not cause extra oxidative load.

The vast majority of circulating copper is transported by an oxidase enzyme called ceruloplasmin, which has antioxidant properties. Ferroxidase enzymatically shows the active state of ceruloplasmin [34, 35]. Various researchers investigated ferroxidase and reported that although it is more dramatic in severe preeclampsia it is higher in preeclamptic pregnancies than in normal pregnancies [36, 37]. Another study states that ceruloplasmin and cholesterol levels can be used to predict the development of preeclampsia in the second trimester. Studies investigating the relationship between OS, antioxidant enzymes, and preeclampsia attribute the increase in ferroxidase activity to increased OS in preeclampsia [36, 37]. As in other studies related to HG and ferroxidase, no significant difference was found in ferroxidase activity when compared to in pregnant women without HG [8, 33]. Ferroxidase level was not significantly different in pregnant women without HG than in the HG group in our study, so this may be one more sign that the oxidant balance is not disturbed.

CAT is an intracellular antioxidant that plays a role in enzymatic defense. It increases during OS to balance the redox reactions. ROS play an important role in pregnancy. However, excessive amounts can override the antioxidant systems and can cause oxidative damage. In the 10th-12th weeks of gestation, ROS levels increase physiologically in pregnant women and this increase is directly proportional to the increase in CAT levels, which is one of the main endogenous antioxidants. However, if there is insufficient antioxidant production, the oxidative balance is disturbed and oxidative damage may contribute to the development of pregnancy disorders [38, 39]. Guney *et al*. found that the CAT level was lower in the group with HG. They reported that it can be explained by the deficiency of antioxidants taken with nutrients [2]. According to Ege *et al*. [33], CAT levels were significantly higher in the HG group and they state that the level of CAT increases during OS to prevent the increase in oxidative radicals. Although CAT levels were significantly higher in the HG group in our study, in light of this information, considering that the pregnant women in the study were at 10-12 weeks, it cannot be concluded that there was extra oxidative load.

The DNI is a marker showing the number of immature granulocytes in human serum. In a limited number of studies, it was used in patient groups with inflammatory processes such as sepsis, acute appendicitis, meningitis, decompensated heart failure, acute gout attack, and acute pancreatitis, and it was thought that it could guide physicians in determining disease severity [19]. In a study published recently, it was mentioned that the DNI was not different in the HG group, but there was an increase in the neutrophil count and neutrophil/lymphocyte ratio in the HG group [40]. No significant change was found in any of the complete blood parameters in our study.

Limitations

Like other studies in the literature, our study has some limitations. The pre-pregnancy oxidative status of the HG group and the control group is not known. In addition, the fetal and neonatal consequences of decreased antioxidants in the HG group are unknown.

CONCLUSION

According to the study, contrary to the literature, HG does not impose an extra burden on maternal oxidative balance. Although there is a decrease in antioxidant levels in terms of thiol/disulfide, we believe that the physiological mechanisms are trying to protect both mother and fetus from possible oxidative complications by keeping the oxidative balance stable. The relationship between oxidative balance and HG complications can be revealed more clearly with fetal/neonatal outcomes.

Ethics approval and consent to participate

All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Republic of Turkey Ministry of Health Ankara City Hospital (Ethics approval reference number: E2-22-2647 and date: 16.10.2022). All procedures were performed according to the Declaration of Helsinki.

Authors' Contribution

Study Conception: GY; Study Design: GY; Supervision: GY, HA, DŞ, ASÖE; Funding: N/A; Materials: GY, SN, GG, ÖE; Data Collection and/or Processing: GY, DO, SN; Statistical Analysis and/or Data Interpretation: GY, DO, SN, GG, ÖE; Literature Review: GY, DO, HA; Manuscript Preparation: GY, DO and Critical Review: DŞ, HA, ÖE, ASÖE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126(3):e12-e24. doi: 10.1097/AOG.0000000000001048.
2. Güney M, Oral B, Mungan T. Serum lipid peroxidation and antioxidant potential levels in hyperemesis gravidarum. Am J Perinatol. 2007;24(5):283-289. doi: 10.1055/s-2007-981429.
3. Kjeldgaard HK, Eberhard-Gran M, Benth JŠ, Nordeng H, Vikanes ÅV. History of depression and risk of hyperemesis gravidarum: a population-based cohort study. Arch Womens Ment Health. 2017;20(3):397-404. doi: 10.1007/s00737-016-0713-6.
4. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11(5):527-359. doi: 10.1093/humupd/dmi021.
5. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007;110(3):695-703. doi: 10.1097/01.AOG.0000278571.93861.26.
6. Aksoy H, Aksoy AN, Ozkan A, Polat H. Serum lipid profile, oxidative status, and paraoxonase 1 activity in hyperemesis gravidarum. J Clin Lab Anal. 2009;23(2):105-109. doi: 10.1002/jcla.20298.
7. Fait V, Sela S, Ophir E, et al. Peripheral polymorphonuclear leukocyte priming contributes to oxidative stress in early pregnancy. J Soc Gynecol Investig. 2005;12(1):46-49. doi: 10.1016/j.jsgi.2004.08.005.
8. Onaran Y, Kafali H, Duvan Cİ, Keskin E, Celik H, Erel O. Relationship between oxidant and antioxidant activity in hyperemesis gravidarum. J Matern Fetal Neonatal Med. 2014;27(8):825-828. doi: 10.3109/14767058.2013.842549.
9. Agarwal A, Gupta S, Sikka S. The role of free radicals and antioxidants in reproduction. Curr Opin Obstet Gynecol. 2006;18(3):325-332. doi: 10.1097/01.gco.0000193003.58158.4e.
10. Osaki S, Johnson DA, Frieden E. The possible significance of the ferrous oxidase activity of ceruloplasmin in normal human serum. J Biol Chem. 1966;241(12):2746-2751.
11. Hellman NE, Gitlin JD. Ceruloplasmin metabolism and function. Annu Rev Nutr. 2002;22:439-458. doi: 10.1146/annurev.nutr.22.012502.114457.
12. Agarwal A, Gupta S, Sekhon L, Shah R. Redox considerations in female reproductive function and assisted reproduction: from molecular mechanisms to health implications. Antioxid Redox Signal. 2008;10(8):1375-1403. doi: 10.1089/ars.2007.1964.
13. Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol. 2005;77(5):598-625. doi: 10.1189/jlb.1204697.
14. Kundi H, Ates I, Kiziltunc E, et al. A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med. 2015;33(11):1567-1571. doi: 10.1016/j.ajem.2015.06.016.
15. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47(18):326-332. doi: 10.1016/j.clinbiochem.2014.09.026.
16. Papageorghiou AT, Prefumo F, Leslie K, Gaze DC, Collinson PO, Thilaganathan B. Defective endovascular trophoblast invasion in the first trimester is associated with increased maternal serum ischemia-modified albumin. Hum Reprod. 2008;23(4):803-806. doi: 10.1093/humrep/den029.
17. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. Am J Pathol. 2003;162(1):115-125. doi: 10.1016/S0002-9440(10)63803-5.
18. Prefumo F, Gaze DC, Papageorghiou AT, Collinson PO, Thilaganathan B. First trimester maternal serum ischaemia-modified albumin: a marker of hypoxia-ischaemia-driven early trophoblast development. Hum Reprod. 2007;22(7):2029-2032. doi: 10.1093/humrep/dem095.
19. Kim H, Kim Y, Lee HK, Kim KH, Yeo CD. Comparison of the delta neutrophil index with procalcitonin and C-reactive protein in sepsis. Clin Lab. 2014;60(12):2015-2021. doi: 10.7754/clin.lab.2014.140528.
20. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 2000;19(4):311-315. doi: 10.1016/s0736-4679(00)00255-9.
21. Erel O. Automated measurement of serum ferroxidase activity. Clin Chem. 1998;44(11):2313-2319.
22. Bradley PP, Priebat DA, Christensen RD, Rothstein G. Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker. J Invest Dermatol. 1982;78(3):206-209. doi: 10.1111/1523-1747.ep12506462.
23. Góth L. A simple method for determination of serum catalase activity and revision of reference range. Clin Chim Acta. 1991;196(2-3):143-151. doi: 10.1016/0009-8981(91)90067-m.
24. Ergin M, Cendek BD, Neselioglu S, Avsar AF, Erel O. Dynamic thiol-disulfide homeostasis in hyperemesis gravidarum. J Perinatol. 2015;35(10):788-792. doi: 10.1038/jp.2015.81.
25. Ustün Y, Engin-Ustün Y, Oztürk O, Alanbay I, Yaman H. Ischemia-modified albumin as an oxidative stress marker in preeclampsia. J Matern Fetal Neonatal Med. 2011;24(3):418-421. doi: 10.3109/14767058.2010.497879.
26. Rossi A, Bortolotti N, Vescovo S, et al. Ischemia-modified albumin in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2013

Oct;170(2):348-51. doi: 10.1016/j.ejogrb.2013.06.037.
27. Longini M, Perrone S, Kenanidis A, et al. ESPR Abstracts: 44 Oxidative Stress in Amniotic Fluid of Pregnancies with Fetal Growth Retardation. Pediatr Res. 2004;56(3):471-471. doi: 10.1203/00006450-200409000-00067.
28. Özdemir S, Kıyıcı A, Balci O, Göktepe H, Çiçekler H, Çelik Ç. Assessment of ischemia-modified albumin level in patients with recurrent pregnancy loss during the first trimester. Eur J Obstet Gynecol Reprod Biol. 2011;155(2):209-212. doi: 10.1016/j.ejogrb.2010.12.004.
29. Cengiz H, Dagdeviren H, Kanawati A, et al. Ischemia-modified albumin as an oxidative stress biomarker in early pregnancy loss. J Matern Fetal Neonatal Med. 2016;29(11):1754-1757. doi: 10.3109/14767058.2015.1061494.
30. Uçkan K, Demir H, Demir C. Maternal serum ischemia-modified albumin (IMA), total-sulphydryl concentrations, and some subclinic inflammatory markers in hyperemesis gravidarum (HG). Taiwan J Obstet Gynecol. 2023;62(1):101-106. doi: 10.1016/j.tjog.2022.10.006.
31. Hung TH, Chen SF, Lo LM, Li MJ, Yeh YL, Hsieh TT. Myeloperoxidase in the plasma and placenta of normal pregnant women and women with pregnancies complicated by preeclampsia and intrauterine growth restriction. Placenta. 2012;33(4):294-303. doi: 10.1016/j.placenta.2012.01.004.
32. Kalva-Borato DC, Ribas JT, Parabocz GC, et al. Biomarkers in Non-Complicated Pregnancy: Insights About Serum Myeloperoxidase and Ultrasensitive C-Reactive Protein. Exp Clin Endocrinol Diabetes. 2019;127(9):585-589. doi: 10.1055/a-0777-2090.
33. Ege S, Bademkiran MH, Peker N, et al. Evaluation of catalase, myeloperoxidase and ferroxidase values in pregnant women with hyperemesis gravidarum. Ginekol Pol. 2019;90(11):651-655. doi: 10.5603/GP.2019.0110.
34. Olivares M, Uauy R. Copper as an essential nutrient. Am J Clin Nutr. 1996;63(5):791S-796S. doi: 10.1093/ajcn/63.5.791.
35. Louro MO, Cocho JA, Tutor JC. Assessment of copper status in pregnancy by means of determining the specific oxidase activity of ceruloplasmin. Clin Chim Acta. 2001;312(1-2):123-127. doi: 10.1016/s0009-8981(01)00607-6.
36. Demir ME, Ulas T, Dal MS, et al. Oxidative stress parameters and ceruloplasmin levels in patients with severe preeclampsia. Clin Ter. 2013;164(2):e83-7. doi: 10.7417/CT.2013.1536.
37. Nikolic A, Cabarkapa V, Novakov Mikic A, Jakovljević A, Stosic Z. Ceruloplasmin and antioxidative enzymes in preeclampsia. J Matern Fetal Neonatal Med. 2016;29(18):2987-2993. doi: 10.3109/14767058.2015.1111333.
38. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. Am J Pathol. 2000;157(6):2111-2122. doi: 10.1016/S0002-9440(10)64849-3.
39. Wu F, Tian FJ, Lin Y, Xu WM. Oxidative Stress: Placenta Function and Dysfunction. Am J Reprod Immunol. 2016;76(4):258-271. doi: 10.1111/aji.12454.
40. Dal Y, Akkuş F, Karagün Ş, Çolak H, Coşkun A. Are serum delta neutrophil index and other inflammatory marker levels different in hyperemesis gravidarum? J Obstet Gynaecol Res. 2023;49(3):828-834. doi: 10.1111/jog.15542.

The European Research Journal 2024;10(6):568-574 Original Article

DOI: https://doi.org/10.18621/eurj.1403401 *Orthopedics and Traumatology*

Retrospective evaluation of functional results and cost analysis of two different anesthesia methods in carpal tunnel syndrome surgery

Bilal Aykaç

Department of Orthopedics and Traumatology, Private Hayat Hospital, Bursa, Türkiye

ABSTRACT

Objectives: The provision of health services at a satisfactory level and low cost is the main objective of all health systems. For this purpose, we evaluated carpal tunnel surgery performed under local anesthesia in the local procedure room and under a laryngeal mask in the operating room in terms of cost analysis. In this way, we aimed to reveal the controllability of health service expenditures and inadequacies in costing.

Methods: A total of 119 patients who underwent local anesthesia (LA) in the local procedure room (Group I) and 45 patients who underwent laryngeal mask anesthesia (LMA) in the operating room (Group II) were retrospectively evaluated. In the calculation of cost analysis, since there were no hospitalization procedures in Group I cases, total costs were calculated only in minutes, multiplied by a coefficient of 7. In Group II cases, total costs were calculated by multiplying total procedure times in minutes by a coefficient of 12 and adding 50 units of hospitalization cost.

Results: Postoperative Quick Disabilities of the Arm, Shoulder, and Hand score is statistically similar in both groups (P=0.714). The operation duration has an average value of 15.39±2.37 in the group of patients who received local anesthesia and 29.71±4.78 in the group treated in the operating room (P<0.001). It has been found that the intervention performed in the operating room is 2.2 times more costly than the local intervention.

Conclusion: Our study is extremely valuable in terms of demonstrating that health service expenditures can be controlled in appropriately selected patients.

Keywords: Cost analyses, carpal tunnel syndrome, anesthesia, local

The main objective of all health systems is to ensure that health services, which are an indispensable part of human life, are satisfactory and cost-effective. However, especially developed countries allocate a significant portion of their gross national product to health expenditures and these expenditures increase year by year [1]. Therefore, calculating hospital and patient costs in health services and revealing the structure of these costs plays an important role in controlling the costs of health care services [2, 3]. At the same time, today's rapid technological advances have manifested themselves in the production of health services, as in all other areas, and as a result, have further increased the costs of hospitals. However, there are insufficient studies and data on the cost of health services. The variety of surgical methods

Corresponding author: Bilal Aykaç, MD.,
Phone: +90 224 225 08 50, E-mail: draykac@gmail.com

How to cite this article: Aykaç B. Retrospective evaluation of functional results and cost analysis of two different anesthesia methods in carpal tunnel syndrome surgery. Eur Res J. 2024;10(6):568-574. doi: 10.18621/eurj.1403401

Received: December 11, 2023
Accepted: February 25, 2024
Published Online: March 25, 2024

and the complexity of calculations are important obstacles in costing [3].

Carpal tunnel syndrome (CTS) is common among the working population, is often attributed to work, and leads to significant health expenditures and major disability costs [4]. Surgical treatment of CTS is one of the most common operations performed on the hand and patients benefit greatly from this surgery. The objective of surgery is to relieve pressure on the median nerve by releasing tension in the transverse carpal ligament. Although there are open, mini-open, and endoscopic surgical methods for this purpose; there is no significant difference in the results of these surgical methods [5]. However, nowadays mini-open carpal tunnel release is a preferable method today due to its positive aspects such as being applicable in a short time in the local operating room under local anesthesia (LA) or in the operation room under anesthesia with a laryngeal mask anesthesia (LMA) [5-7].

At this point, we evaluated carpal tunnel surgery, which we frequently perform under local anesthesia in the local procedure room and the operating room under anesthesia with a laryngeal mask, to make cost analysis and to be used in planning and control processes. Our objective was to demonstrate both the ability to manage health service expenses and the deficiencies in cost estimation.

METHODS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine on June 16, 2021, under the reference number 2011-KAEK-26/384.

In this retrospective study, we focused on patients who underwent surgery for CTS between June 2018 and January 2023 at the Orthopedics and Traumatology clinic of our hospital. Patients were selected based on a confirmed diagnosis of CTS through electromyography (EMG) following a clinical examination and a lack of response to conservative treatment. Patients who received anesthesia other than LA or LMA, who had bilateral or additional hand surgery in the same session, who had CTS after fracture, who had peripheral neuropathy, who had revision surgery, who had different surgery techniques other than mini-open and who did not have a QDASH score were excluded from the study. A total of 164 cases were included in our study, with 119 patients undergoing surgery under local anesthesia (LA) in the local procedure room and 45 patients receiving surgery under laryngeal mask anesthesia (LMA) in the operating room. Patients were initially categorized into two groups based on the anesthesia method employed (LA or LMA).

From the patient registration system, we collected data on age, gender, surgery date, type of anesthesia, postoperative complications, total length of hospital stay, total follow-up times, and total surgical costs for all cases. Preoperative Quick Disabilities of the Arm, Shoulder, and Hand (QDASH) scores of all patients included in the study were retrospectively examined and recorded.

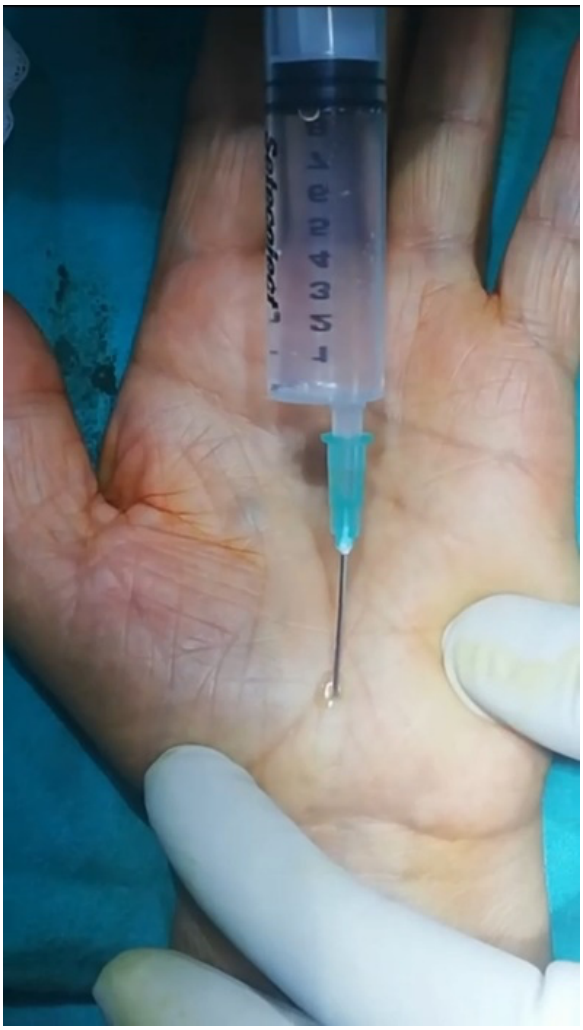


Fig. 1. Local anesthesia application on carpal tunnel.

Surgical Procedures

Patients in Group I (LA) had their surgical site cleaned with povidone-iodine while wearing an arm cuff. The surgical area was then draped with a sterile covering. Subsequently, 5 cc of Prilocaine (2%) was injected into the incision site, and another 5 cc was injected into the carpal tunnel (Fig. 1). Sedation was not administered to any patient. The surgical procedure commenced within a minute of local anesthesia, following tourniquet application at 250 mmHg pressure with the extremity elevated immediately before incision.

Patients in Group II (LMA) were positioned supine on the operating table, and LMA was administered by an anesthesiologist while monitoring the patient. Tourniquet application at 250 mmHg pressure, with elevation of the surgical site, was followed by cleaning the surgical area with povidone-iodine and draping it with a sterile cover before the surgery began.

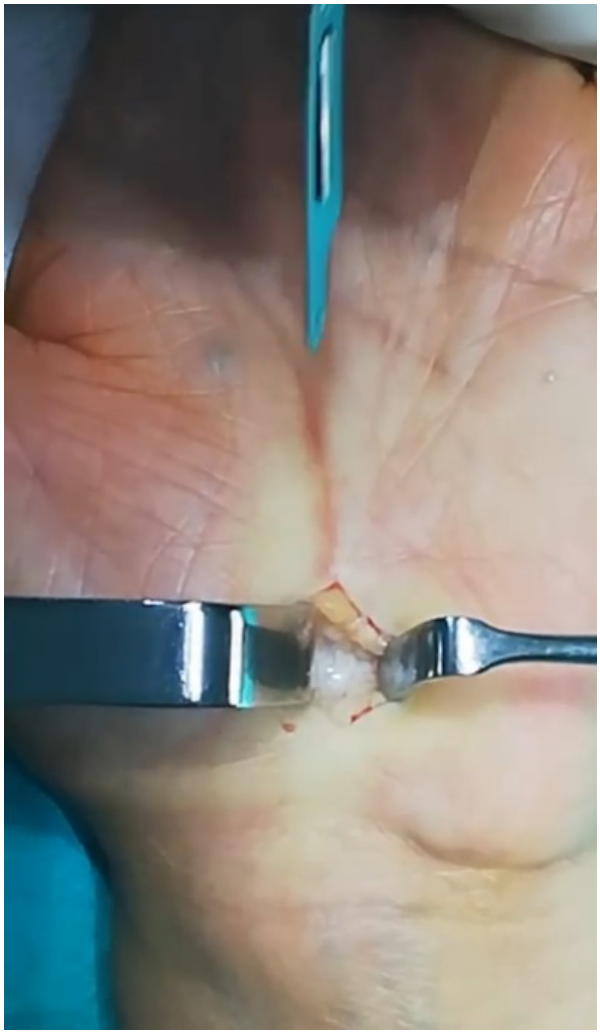


Fig. 2. Standard mini-incision applied to patients.

After these preparatory phases, the same surgical team performed the surgery in both groups. A roughly 2 cm incision was made distally to the flexor line of the volar aspect of the wrist (Fig. 2). Blunt dissection was carried out up to the flexor retinaculum, and sharp dissection opened the flexor retinaculum. The median nerve was protected upon its exposure, and the flexor retinaculum was released proximally and distally. Hemostasis was maintained, and the skin incision was primarily sutured, followed by a sterile dressing application.

Wrist and finger movements were permitted in the early postoperative period. Patients in both groups underwent outpatient follow-ups at the 2-week postoperative mark, with suture removal occurring between days 10 and 15. Preoperative and 3-month postoperative evaluations were conducted for both patient groups using QDASH functional scores to assess surgical success and determine study eligibility. There was one patient in each group who needed surgery again. One patient in the LA group underwent surgery due to a superficial wound infection. The other patient in the LMA group needed surgery due to the persistence of complaints because of insufficient and no additional complications were observed in either patient.

Cost Analysis

To perform a cost analysis, we initially calculated minute costs for both the local (LA) and operating rooms (LMA). This involves determining room usage costs per minute, staff numbers, and unit costs for drugs and consumables used [8]. We aimed to create currency-independent coefficients by calculating room usage costs per minute and determining staff numbers and unit costs for drugs and consumables. In the time calculation, the patients' room entry and exit times were recorded. The standard costs of the rooms (local (LA) and operating room (LMA)); set usage and consumables were considered the same. The drugs used for both anesthesia methods were administered standardly to the patients in each group. Standard 2 personnel were used for local anesthesia and standard 4 personnel were used for general anesthesia. In the cost calculation, we determined coefficients of 7 units per minute for LA cases and 12 units per minute for LMA cases. While determining the coefficients; Minute

costs were calculated based on the monthly expenses of the rooms and staff. In the calculation, staff salaries and monthly usage costs of both rooms were considered equal. The cost per minute of two rooms was found to be 7/12 in proportion. Additionally, in the LMA group; the 4-hour hospital stay was calculated by standardizing the drugs used during hospitalization and for anesthesia. According to this calculation, an additional cost of 50 units was found in the LMA group, proportional to the cost of 7 units. As a result, in LA cases, total costs were calculated by multiplying the total procedure time by a coefficient of 7, and in LMA cases total costs were calculated by multiplying the total procedure time in minutes by a coefficient of 12 and adding 50 units to account for hospitalization costs.

Statistical Analysis

The data analysis was conducted using IBM SPSS Statistics Standard Concurrent User Version 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were reported, including counts (n), percentages (%), means±standard deviations, and median (minimum and maximum) values. The normality of numerical data distribution was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was employed to compare single-measure numerical variables between the local anesthesia and operating room groups. Categorical variables were compared using the Pearson Chi-square test. A significance level of $P<0.05$ was deemed statistically significant.

RESULTS

The age of patients in the local anesthesia group was significantly lower than that of patients in the surgical group. (P=0.003). Gender distribution was similar in both groups (p=0.866). QDASH scores were statistically similar between the LA and LMA groups for both preoperative, postoperative, and delta values groups (P=0.801).

Preoperative QDASH scores averaged 63.34±6.30 in the LA group and 63.11±7.05 in the LMA group, showing no statistically significant difference (P=0.974). Postoperative QDASH scores were 4.46±5.68 in the LA group and 4.07±2.11 in the LMA group, also with no statistically significant difference (P=0.714). The QDASH score delta (preoperative-postoperative) was 58.87±7.36 in the LA group and was 59.03±7.03 in the LMA group, with no statistically significant difference (P=0.801).

The operation duration was significantly shorter in the LA group, with an average of 15.39±2.37 minutes, compared to 29.71±4.78 minutes in the LMA group ($P<0.001$). It was determined that all of the 4-hour additional hospital stays were in the LMA group.

The unit cost was lower in the LA group, averaging 7±0.09, in contrast to 12±0.001 in the LMA group ($P<0.001$).

Furthermore, the total cost was significantly lower in the LA group, averaging 107.76±16.61, as opposed to 345.11±75.98 in the LMA group ($P<0.001$) (Table 1).

This indicates that interventions performed in the LMA are 2.2 times more costly than those conducted with LA. Superficial infection was encountered in one patient in the LA group and inadequate decompression complications were encountered in one patient in the LMA group. Both patients recovered with repeated surgeries.

DISCUSSION

The existing literature does not provide a consensus on the ideal anesthesia method or surgical approach for the treatment of carpal tunnel syndrome. The choice of anesthesia and surgical approach can often depend on patient-specific factors and surgeon preferences. However, the primary objective remains consistent: achieving the most successful clinical outcome with minimal complications. At this juncture, surgeons select the surgical intervention that aligns most effectively with the patient's needs.

The surgical technique and anesthesia method used in carpal tunnel release (CTR) vary depending on surgeon preference and patient factors [7]. The age difference between the two groups in our study can be explained by the patients' own anesthesia preferences. No criterion was chosen in terms of age, and no study showing a relationship between anesthesia preference and age was found in the literature. A prospective study showed that age, gender or occupation did not affect the outcome of carpal tunnel decompression in

Table 1. Comparison of other variables by anesthesia groups

	Local anesthesia	Larengeal mask anesthesia	Test value	P value
Age (years)	54.56±12.99 56 (26-88)	48.37±10.39 47 (32-76)	*z*=3.003	**0.003**
Gender, n (%)				
Male	94 (72.9)	35(27.1.)	χ^2=0.029	0.866
Female	25(71.4)	10(28.6)		
QDASH preoperative	63.34±6.30 63.60 (48.7-80)	63.11±7.05 63.5 (44.6-72.7)	*z*=0.033	0.974
QDASH postoperative 3. months	4.46±5.68 4.5 (0-54)	4.07±2.11 4.5 (0-9)	*z*=0.367	0.714
QDASH delta	58.87±7.36 60 (14.7-73.2)	59.03±7.03 60.2 (42.3-68.2)	*z*=0.252	0.801
Operation time (min)	15.39±2.37 15 (10-25)	29.71±4.78 30 (14-40)	*z*=9.366	**<0.001**
Unit cost	7.00±0.001 7 (7-7)	12.0±0.001 12 (12-12)	*z*=12.666	**<0.001**
Total cost	107.76±16.61 105 (70-175)	345.11±75.98 360 (168-480)	*z*=9.479	**<0.001**
Hospital total cost	107.76±16.61 105 (70-175)	391.33±87.18 410 (218-530)	*z*=9.475	**<0.001**

Data are shown as mean±standard deviation or median (minimum-maximum) or n (%). QDASH=Quick Disabilities of the Arm, Shoulder, and Hand, %=Row Percent, z=Mann-Whitney *U* test, χ^2=Chi-Square test statistics.

a series of 608 carpal tunnel decompressions, as assessed by the Boston carpal tunnel score [9].

Regardless of which anesthesia is used during a patient's carpal tunnel surgery, the general patient consensus tends toward high rates of satisfaction with the surgery and a proclivity to choose that treatment method again, if necessary. Garrett *et al*. [10] have found no difference in terms of postoperative functional results and complications between local and sedated anesthesia applications. In our study, although there was no postoperative functional difference between the two groups, one complication was encountered in each group and recovery was achieved with repeated surgery.

In addition, various anesthetic modalities are commonly used during CTR, including general, regional, and local anesthesia. Local anesthesia is associated with shorter operative times, higher patient satisfaction scores, and equivalent functional outcomes [7, 11, 12]. In our study, significantly shorter procedure times were achieved in local anesthesia compared to LMA.

CTR under local anesthesia can be safely performed in an office-based setting with minor procedure field sterility and no prophylactic antibiotics. More than 70% of hand surgeons in Canada use local anesthesia for CTR with similar reported outcomes. In addition to cost savings, local anesthesia is associated with shorter surgical wait times and increased convenience [7]. Previous studies estimate the potential for anywhere from 30% to 80% in total cost reduction by shifting appropriate procedures toward ambulatory surgery centers and in-office procedure rooms. The present study evidenced only $390 in anesthesia cost savings; however, with an estimated 700,000 carpal tunnel releases occurring per year, this modest cost reduction would compound to nearly $300 million in

cost savings if local procedures are more widely implemented [13]. In our study, the fact that the LMA group is 2.2 times more costly than the LA group is also compatible with the literature, and we think that it is advantageous to prefer local applications in CTS procedures, primarily in terms of cost.

The practice of outpatient surgery offers several advantages, including reduced patient wait times for procedures, fewer complications associated with anesthesia, and decreased healthcare expenditures due to factors such as the absence of mandatory blood tests and additional consultations [14]. In this regard, the outcomes of our study reinforce the existing literature by highlighting the potential for substantial cost savings in healthcare expenditures associated with carpal tunnel surgery performed under LA.

Evaluating the efficiency of hospitals and healthcare workers necessitates a comprehensive assessment of financial calculations, with a clear distinction between standard and actual costs. Patients diagnosed with the same medical condition may incur vastly different diagnostic and treatment expenses. Introducing cost analysis into healthcare services is challenging, and it remains a significant obstacle to fully understanding the underlying reasons for these variations. While it's acknowledged that human health cannot be measured solely in monetary terms, it is undeniable that meeting the need for good health carries a substantial cost in today's world.

Today, assessing healthcare policy content, which evolves in response to research and development in human resources, necessitates a foundation rooted in cost research. Simultaneously, the central goal of hospital cost management is to deliver healthcare services with the highest quality and quantity at the lowest possible cost [1, 15]. In this context, cost studies often center on surgical procedures, which are generally cost-intensive. Nevertheless, as demonstrated in our study, when the surgical procedure and materials used are identical, the differentiation lies solely in the location where the healthcare service is provided. In this context, the significance of healthcare investment can be assessed more distinctly. Our study, therefore, unveils the extent to which cost discrepancies arise in surgical practice across two distinct environments. By comparing the utilization of operating rooms and staff, two critical cost categories in healthcare expenditures, while applying the same surgical technique and materials, we shed light on the multifaceted nature of healthcare costs.

Limitations

The study is conducted at a single center which may limit the generalizability of the findings to a broader population. Different hospitals and healthcare systems may have varying cost structures and patient populations.

CONCLUSION

In our study, we show that healthcare expenditures can be controlled in selected patients with different anesthesia applications in two different areas within the hospital. Such studies can provide important information for health services planning and management. In this way, we think that our study is valuable in that it can be used in cost analysis and planning and supervision processes in today's world where health expenditures have reached very large dimensions.

Authors' Contribution

Study Conception: BA; Study Design: BA; Supervision: BA; Funding: BA; Materials: BA; Data Collection and/or Processing: BA; Statistical Analysis and/or Data Interpretation: BA; Literature Review: BA; Manuscript Preparation: BA and Critical Review: BA.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Carrin G. Social health insurance in developing countries: a continuing challenge. Int Soc Secur Rev. 2002;55(2):57-69. doi: 10.1111/1468-246X.00124.
2. Nuckols TK, Dworsky M, Conlon C, et al. The quality of occupational healthcare for carpal tunnel syndrome, healthcare expenditures, and disability outcomes: A prospective observational study. Muscle Nerve. 2023;67(1):52-62. doi: 10.1002/mus.27718.

3. Drechsler D. Jütting Jp. Empirical and economic underpinnings. Global marketplace for private health insurance: Strength in numbers. Eds: Preker As. Zweifel P. Schellekens. The World Bank Washington, D.C. 2010:27-99.
4. Luckhaupt SE, Dahlhamer JM, Ward BW, Sweeney MH, Sestito JP, Calvert GM. Prevalence and work−relatedness of carpal tunnel syndrome in the working population, United States, 2010 National Health Interview Survey. Am J Ind Med. 2013;56(6):615−624. doi: 10.1002/ajim.22048.
5. Zhang S, Vora M, Harris AH, Baker L, Curtin C, Kamal RN. Cost-Minimization Analysis of Open and Endoscopic Carpal Tunnel Release. J Bone Joint Surg Am. 2016;98(23):1970-1977. doi: 10.2106/JBJS.16.00121.
6. D'Arcy CA, McGee S. The rational clinical examination. Does this patient have carpal tunnel syndrome? JAMA. 2000;283(23):3110-3117. doi: 10.1001/jama.283.23.3110.
7. Foster BD, Sivasundaram L, Heckmann N, et al. Surgical Approach and Anesthetic Modality for Carpal Tunnel Release: A Nationwide Database Study With Health Care Cost Implications. Hand (N Y). 2017;12(2):162-167. doi: 10.1177/1558944716643276.
8. Kazmers NH, Presson AP, Xu Y, Howenstein A, Tyser AR. Cost Implications of Varying the Surgical Technique, Surgical Setting, and Anesthesia Type for Carpal Tunnel Release Surgery. J Hand Surg Am. 2018;43(11):971-977.e1. doi: 10.1016/j.jhsa.2018.03.051.
9. Ibrahim T, Majid I, Clarke M, Kershaw CJ. Outcome of carpal tunnel decompression: the influence of age, gender, and occupation. Int Orthop. 2009;33(5):1305-1309. doi: 10.1007/s00264-008-0669-x.
10. Via GG, Esterle AR, Awan HM, Jain SA, Goyal KS. Comparison of Local-Only Anesthesia Versus Sedation in Patients Undergoing Staged Bilateral Carpal Tunnel Release: A Randomized Trial. Hand (N Y). 2020;15(6):785-792. doi: 10.1177/1558944719836237.
11. Lalonde D. Minimally invasive anesthesia in wide awake hand surgery. Hand Clin. 2014;30(1):1-6. doi: 10.1016/j.hcl.2013.08.015.
12. Sørensen AM, Dalsgaard J, Hansen TB. Local anaesthesia versus intravenous regional anaesthesia in endoscopic carpal tunnel release: a randomized controlled trial. J Hand Surg Eur Vol. 2013;38(5):481-484. doi: 10.1177/1753193412453664.
13. Via GG, Esterle AR, Awan HM, Jain SA, Goyal KS. Comparison of Local-Only Anesthesia Versus Sedation in Patients Undergoing Staged Bilateral Carpal Tunnel Release: A Randomized Trial. Hand (N Y). 2020;15(6):785-792. doi: 10.1177/1558944719836237.
14. Kazmers NH, Presson AP, Xu Y, Howenstein A, Tyser AR. Cost Implications of Varying the Surgical Technique, Surgical Setting, and Anesthesia Type for Carpal Tunnel Release Surgery. J Hand Surg Am. 2018;43(11):971-977.e1. doi: 10.1016/j.jhsa.2018.03.051.
15. Becker GS. The Market For Health Insurance. Essentials Of Health Economics. Eds: Dewar Dm. Jones And Bartlett Publishers, 2010: pp. 31-40.

The European Research Journal 2024;10(6):575-587 Original Article

DOI: https://doi.org/10.18621/eurj.1454763 *Public Health Nursing*

A bibliometric analysis of studies conducted over the last 10 years on cardiovascular disease risk identification and prevention in primary care

Ayşe Dağıstan Akgöz

Department of Public Health Nursing, Akdeniz University, Faculty of Nursing, Antalya, Türkiye

ABSTRACT

Objectives: This bibliometric analysis was conducted to determine the trends of studies on cardiovascular disease risk identification and prevention in primary care from 2013 to 2024 and visualize the latest developments.

Methods: The data were collected in February-March 2024 from the database "Web of Science Core Collection," the analysis was carried out using the VOSviewer program. The change in the number of publications of the published articles by year, author, country, and institution citation analyses, country, institution, and author collaboration analyses, journal and author co-citation analyses, and keyword analyses were evaluated.

Results: Five hundred and ninety-two authors from 64 countries and 377 institutions contributed to 443 studies published in 80 journals between 2013 and 2024 on determining and preventing cardiovascular disease risk in primary care. "BMC Family Practice" was the journal in which most articles were published, and "Circulation" was the most cited. The first three countries that support published articles most are the United States, England, and Australia. Focusing on the topics "blood-pressure control", "coronary-artery calcium", "physician-pharmacist collaboration", "low-density lipoprotein cholesterol", "health-risk assessment", "pollution", "primary care", "coronary heart disease", "prevention", "cardiovascular disease" and "mortality" will help fill the gap in the field.

Conclusions: This bibliometric analysis has shown increasing interest in studies related to cardiovascular disease risk and prevention in primary care. Primary prevention guidelines are important resources in addressing risk factors. Global collaborations and long-term studies are necessary in this field, led by developed countries with a high disease burden.

Keywords: Cardiovascular diseases, bibliometrics, primary care, CVD risk, risk identification, risk prevention, data visualization

Cardiovascular diseases (CVD), the most common non-communicable disease worldwide, are the general name for a group of disorders of the heart and blood vessels and conditions such as coronary heart disease, cerebrovascular disease, and rheumatic heart disease [1]. Cardiovascular diseases account for the death of nearly 18 million people globally each year. The occurrence of cardiovascular

Corresponding author: Ayşe Dağıstan Akgöz, PhD.,
Phone: +90 242 310 61 03 ext. 2917, E-mail: aysedagistan@akdeniz.edu.tr

How to cite this article: Dağıstan Akgöz A. A bibliometric analysis of studies conducted over the last 10 years on cardiovascular disease risk identification and prevention in primary care. Eur Res J. 2024;10(6):575-587. doi: 10.18621/eurj.1454763

Received: March 18, 2024
Accepted: June 6, 2024
Published Online: July 9, 2024

diseases has almost doubled in the past two decades, according to the World Health Organization (WHO) [2]. The leading causes of these diseases include risk factors such as high blood pressure, obesity, smoking, a sedentary lifestyle, and an unhealthy diet [3].

Public health strategies to reduce cardiovascular disease morbidity and mortality include population-level risk factor reduction and individual-based primary and secondary prevention and treatment. Cardiovascular disease risk refers to the likelihood of experiencing fatal or nonfatal CVD events, such as the risk of myocardial infarction or stroke, within the next decade [4]. Individual-based primary prevention targets high-risk groups and prevents the onset of CVD by reducing the risk factor. Secondary prevention and treatment aims at early diagnosis and treatment to prevent disease progression in people with established CVD [5].

To prevent cardiovascular diseases, it is necessary to promptly identify people at high risk for primary prevention, which includes healthy nutrition and lifestyle interventions, or for treatments, including drug interventions. Over the past two decades, numerous prediction models have been developed that mathematically combine multiple predictors to predict the risk of developing CVD [6]. For example, tools such as Framingham [7], SCORE [8], and QRISK (9) are among the most commonly used. Some of these prediction models are included in the clinical guidelines for therapeutic management. Health policymakers are increasingly advocating these models [6].

The national and international guidelines published for the prevention of cardiovascular diseases recommend lifestyle changes such as healthy eating, increasing physical activity, quitting smoking and losing weight [4, 9-12]. Finding ways to implement proven interventions to reduce CVD risk factors in at-risk populations can reduce CVD health inequalities in primary care [13]. Community-based CVD prevention programs are another effective method recommended to reduce medical care costs and the disease burden attributable to CVDs [14]. Therefore, there has been a shift towards community-based programs to prevent CVD in recent years. Thanks to this approach, even minor improvements in general risk factors can significantly decrease the CVD burden [15]. Studies conducted in this field over the last ten years show that community-based interventions improve CVD risk factors, especially by reducing blood pressure, serum LDL-C and triglyceride levels, obesity indices, and blood sugar, leading to a successful improvement in CVD risk factors. It is also emphasized that the impact of these programs on CVD varies depending on the type of intervention and different cultural and physical environments [16].

In recent years, the rapid increase and change in the direction of studies on determining and preventing CVD risk in primary care make it difficult for researchers to follow the results of current studies. Therefore, there is an increasing need to identify trends, map recent developments, and identify research gaps regarding CVD risk identification and prevention in primary care. In addition, it is essential to evaluate the studies carried out in this field in recent years to increase confidence in the results of risk identification and prevention studies on the subject and to contribute to primary healthcare policies.

Bibliometric analysis is an analytical method used to obtain formal and quantitative data about a field's current status. It makes it easier to monitor academic trends through visualization software. The bibliometric approach aims to provide quantitative data about research performance [17]. The researchers' experiences and knowledge inspire the comments based on these metrics in the field. Researchers use bibliometric analysis for various reasons, including uncovering emerging trends in article and journal performance, patterns of collaboration and research components, and exploring the intellectual structure of a particular field in the existing literature [18]. In other words, bibliometric analysis is used to map scientific knowledge in a field by making sense of large volumes of unstructured data. Therefore, well-done bibliometric studies can create solid foundations for advancing a field in new and meaningful ways. They enable academics to gain a general perspective from a single source, identify knowledge gaps, derive new ideas for research, and position their research [19].

As far as is known in the literature, no bibliometric analysis is related to the determination and prevention of CVD risk performed in primary care. This bibliometric analysis reflects the current evidence by analyzing the bibliometric properties of articles published on CVD risk identification and prevention in primary care. It allows researchers and policymakers to obtain information about the structure of their field, under-

stand the research gaps, and evaluate future studies on CVD risk identification and prevention in primary care. It will contribute to developing innovative ideas regarding studies.

Research Questions

•What is the distribution of publications and citations over the years?

•What are the most influential publications in the field on the subject?

•What are the most productive journals in the relevant field?

•How are publications distributed by country and what are the collaborations between countries?

•How is the analysis of keywords used by authors in publications?

•What are the trending topics of publications by year?

•What is the thematic map of the publications?

METHODS

Purpose

This bibliometric analysis was conducted to identify the trends of studies on cardiovascular disease risk identification and prevention in primary care from 2013 to 2024 and visualize the latest developments.

Design

This study conducted a bibliometric analysis of studies on cardiovascular disease risk identification and prevention in primary care. Bibliometric analysis is a powerful statistical tool that allows quantitative and qualitative evaluation of articles [19].

Data and Analysis

Different tools and software are used to perform bibliometric analysis in the literature. The VOSviewer program was used in this study. VOSviewer is a software tool for creating maps based on data sets and visualizing and exploring these maps [20]. The analysis was performed on articles published between 2013 and 2024. Only documents identified as articles in Web of Science were included in the analysis; other documents such as recommendations, guidelines, reviews, letters, or editorials were excluded. The research focused on original articles to seek new contributions to the literature. The reason for not including non-English studies is that language barriers may complicate the data processing and analysis process. It was excluded to avoid technical difficulties due to language differences when analyzing the data.

On 04.03.2024, 533 results were found in the search by selecting "all fields" in Web of Science with the keyword sequence in Table 1. Four hundred forty-eight journal articles from different disciplines, eight

Table 1. Keyword sequence

Category	Derivation
Cardiovascular disease	Cardiac Events, Heart Diseases
CVD	Cardiac disease
Risk assessment	Risk Evaluation
	Risk Estimation
	Risk Assessments
	Risk Analyses
Primary prevention	Risk Protection
Primary Care	Preventive health
	Public Health
	Public Health Practice
	Primary health care

(TS=(“* Cardiovascular disease*” OR “*CVD*” OR “Cardiac Events” OR “Heart Diseases” OR “Cardiac disease”)) AND (TS=(“Risk evaluation” OR “Risk estimation” OR “Risk Assessments” OR “Risk Analyses” OR “Risk assessment”)) AND (TS=(“ Primary Care” OR “Preventive health” OR “Public Health” OR “Public Health Practice” OR “Primary health care”))

editorial content, 76 early appearance studies, 75 review articles, and four book-type works were accessed, according to years, the oldest being 2013 and the newest being 2024. In terms of disciplines, the vast majority of the studies were conducted in the fields of Medicine (134), Public Health (108), Cardiovascular Systems (88), Primary health care (56), Peripheral Vascular Disease (34), Endocrinology Metabolism (31), Health Science Services (25), Environmental Sciences (22). Out of 533 results, 443 original articles were analyzed using author, citation, journal, country, institution, and keyword analysis.

In order to expand the scope of the study with more analytical techniques, Bibliometrix software was used to reveal the research focuses (trend topics) and thematic trends (thematic map) of the studies [21].

Ethics

Since this study was not conducted on any individual and used document analysis as the data collection method, ethics committee approval is not required.

RESULTS

The number of publications of the 443 included studies varies between 3 and 47 by year. The most publications (n=47, 10.6%) were made in 2016 and 2020, and the least were published in 2012 (excluding 2024=3 articles). The number of articles by year is given in Fig. 1.

Co-authorship of Authors

In the co-authorship analysis of the authors, a network diagram was created to determine the most connected and collaborative authors by selecting the criteria of at least 1 document and at least 1 citation. According to the analysis made among the names with the highest connections, eight are combined in a single cluster and have 92 connections. It is also seen that the most cited authors (Roger S. Blumenthal with 8100 citations, Erin D. Michos with 8100 citations, and Michelle A. Albert with 9039 citations) are not the most connected. The authors who produce the most documents do not appear to be among the most connected either (Rod Jackson, Sue Wells, and Andrew Kerr, respectively) (Fig. 2.).

Citation Analysis of Authors

To identify citation networks, a network map was created for author citation analysis with the criteria of at least 1 document and at least 1 citation. In the analysis made on 592 units that were seen to be connected, a total of 20 clusters, 7580 connections and a total connection strength of 11234 were detected. The most cited authors were Roger S. Blumenthal with 8100 citations, Erin D. Michos with 8100 citations, and Michelle A. Albert with 9039 citations. In terms of total connection strength, Rod Jackson ranks first with

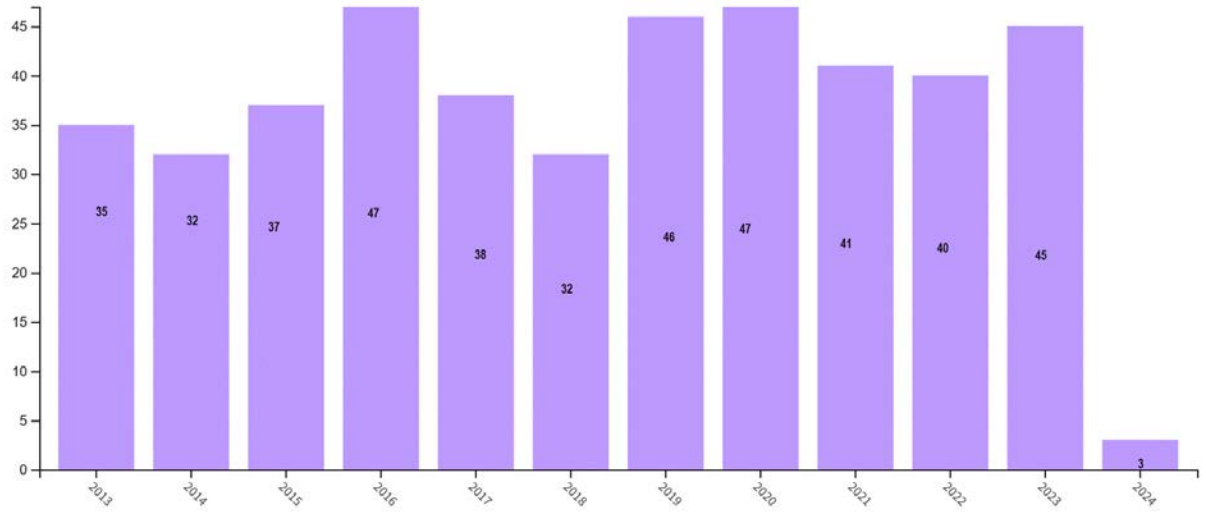


Fig. 1. The number of publications in 2013-2024.

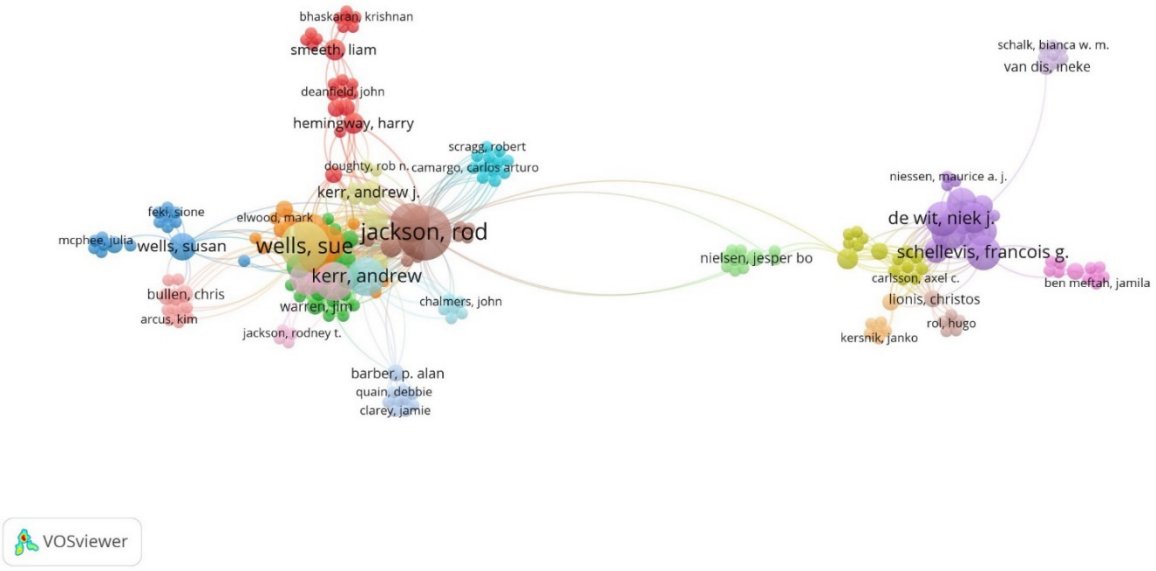


Fig. 2. **Co-authorship of authors.**

626 connections, Sue Wells ranks second with 576 connections, and Matire Harwood ranks third with 436 connections (Fig. 3).

Citation Analysis of Countries

In order to create a network map of the citations received by publications according to their country of origin, an analysis was made on 64 observation units that have a relationship between them within the scope of the criterion of publishing at least 1 document and receiving 1 citation by a country. Eight clusters, 213 connections, and 458 total connection strengths were identified. The countries with the most citations were the USA (11765 citations), Ireland (8067 citations) and Italy (5653). Regarding total connection power, the USA ranks first, Australia ranks second, and the Netherlands ranks third. In terms of the number of works, the order is as follows: USA (127 publications),

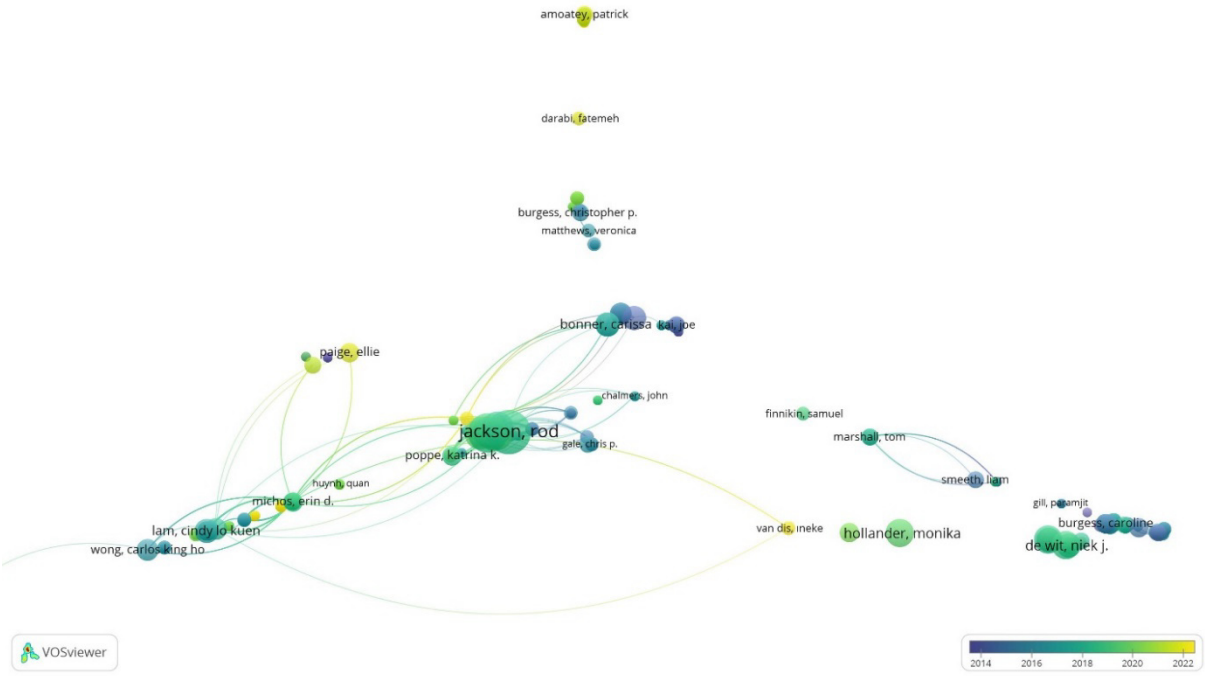


Fig. 3. **Citations of authors.**

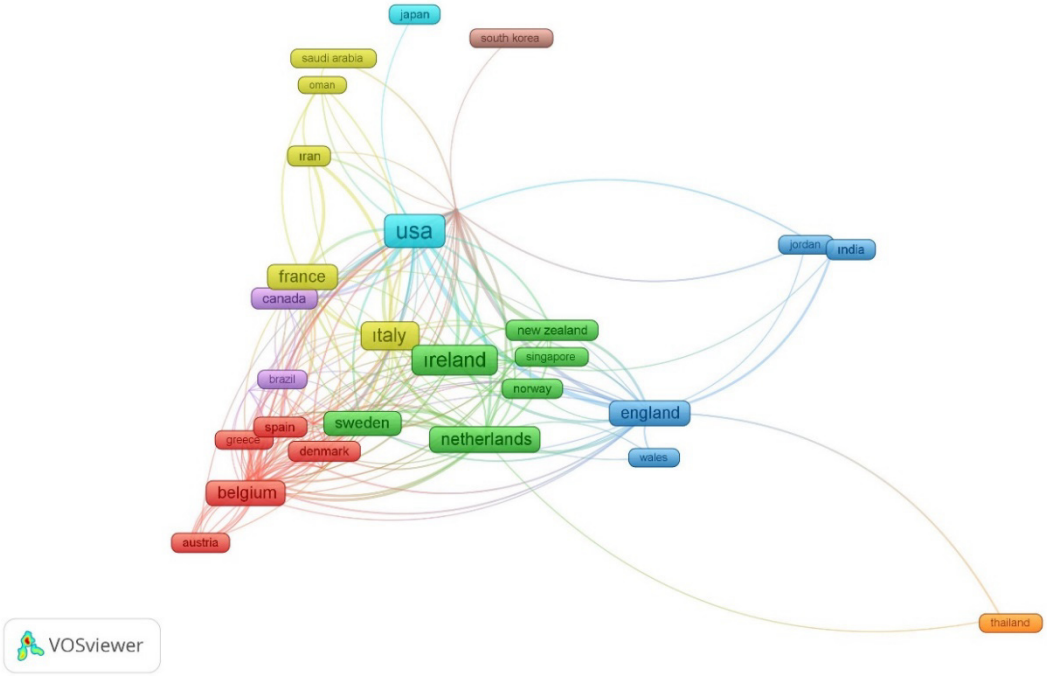


Fig. 4. **Citations of countries.**

England (93 publications) and Australia (48 publications) (Fig. 4).

Citation Analysis of Organizations

To create a network map of organizational citations, an analysis was made on 377 observation units that have a relationship with each other within the scope of the criteria of publishing at least one document and receiving 1 citation by an organization. While Auckland University (31 publications), Cambridge University (15 publications), Sydney University (14) are represented by publications, the address organizations of the most cited publications are The University of North Carolina (8078 citations), North-

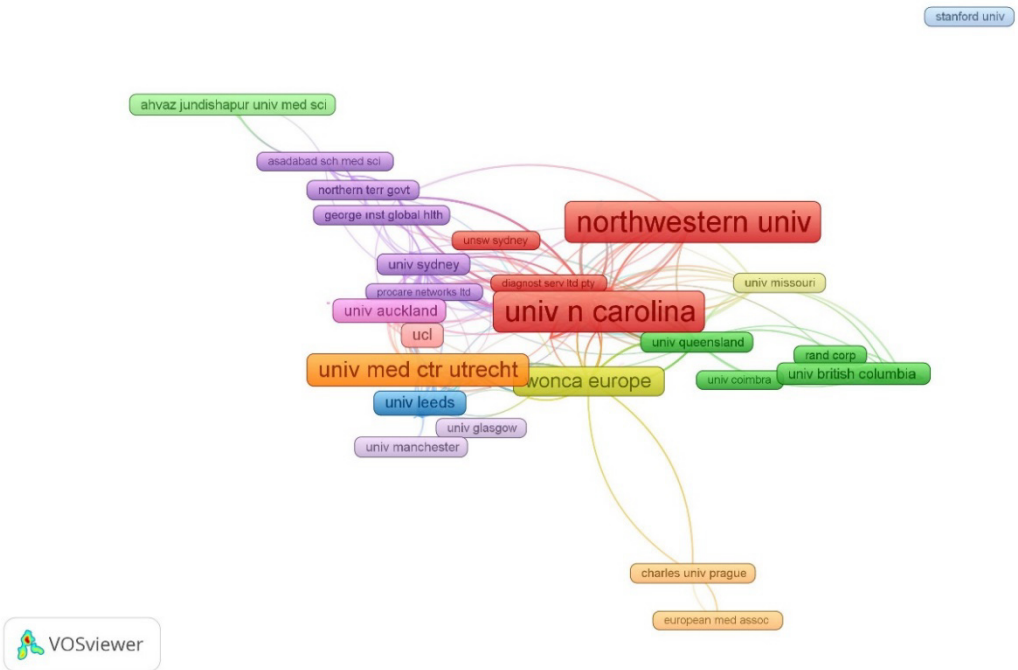


Fig. 5. **Citation of organizations.**

Table 2. Top 5 most cited publications

Puplication title	Author	Year	Journal	Total citations
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines	Arnett *et al.* [26]	2019	Circulation	7886
2016 European Guidelines on cardiovascular disease prevention in clinical practice	Piepoli *et al.* [9]	2016	Atherosclerosis	5320
Global, Regional, and National Comparative Risk Assessment of 84 Behavioural, Environmental and Occupational, and Metabolic Risks or Clusters of Risks for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017	GBD 2017 Risk Factor Collaborators [29]	2018	Lancet	2686
Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013	GBD 2013 Risk Factors Collaborators [30]	2015	Lancet	1898
Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States	Micha *et al.* [31]	2017	JAMA	677

Western University (8051 citations) and Johns Hopkins University (8031 citations). Of 18 clusters, 2690 connections and total connection strength were determined as 3298 (Fig. 5).

Citation Analysis of Documents

According to the analysis made with 114 units selected with the criterion of having received at least one citation and had connections between them, 18 clusters and 144 connections were obtained. When we look at the articles published on determining and preventing cardiovascular disease risk in primary care, it can be seen that Arnett (2019), Piepoli (2016), and Stanaway (2018) are among the top three most cited documents (Table 2).

Citation Analysis of Journals

According to the analysis made with 231 units with links between them, selected with the criterion of having at least one citation, 15 clusters, and 148 links were obtained. When we look at the articles published on determining and preventing the risk of cardiovas-

Table 3. Top 5 journals with the most citations and publications

	Journal	Number of citations		Journal	Number of publications
1	Circulation	8130	1	BMC Family Practice	12
2	Lancet	4745	2	BMC Public Health	12
3	European Heart Journal	3138	3	Plos One	11
4	Atherosclerosis	2202	4	British Journal of General Practice	11
5	Lancet Diabetes & Endocrinology	788	5	BMJ Open	10

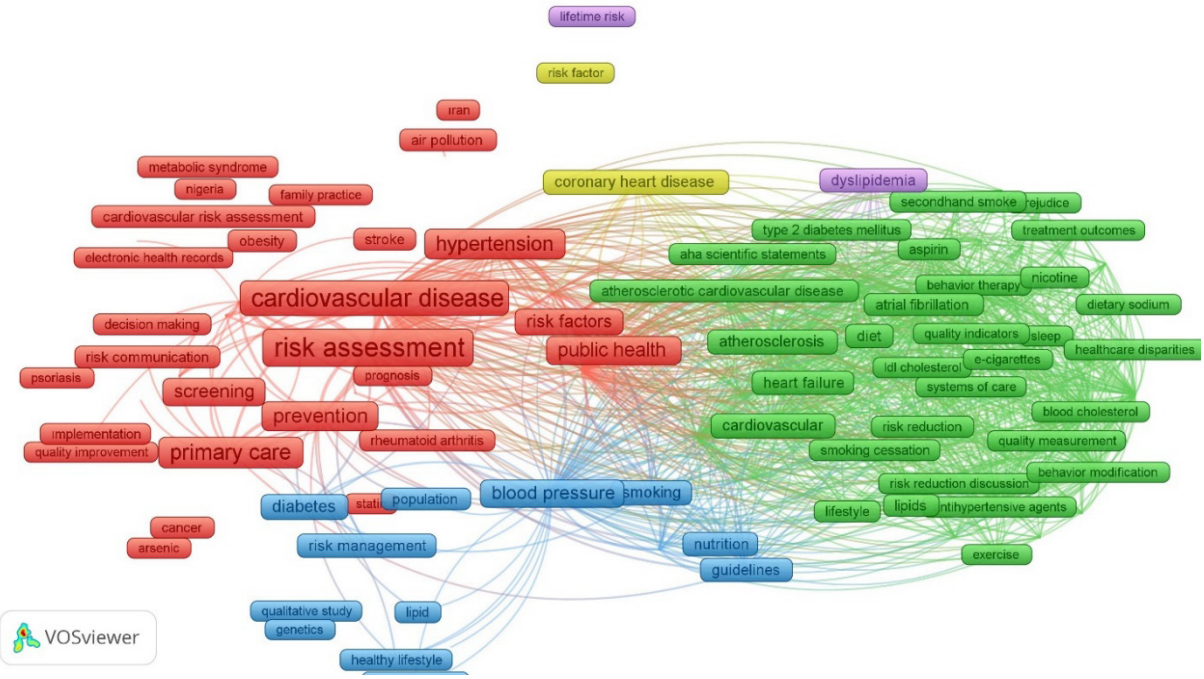


Fig. 6. **Co-occurrence of all keywords.**

cular disease in primary care, the most cited journals are Circulation and Lancet, which appears to be in the top three of the European Heart Journal. The journals with the most publications on the subject are BMC Family Practice, BMC Public Health, and Plos One, respectively (Table 3).

Co-occurrence of All Keywords

When we look at the most frequently used keywords in documents on determining and preventing cardiovascular disease risk in primary care, risk assessment with 95 repetitions, cardiovascular disease with 77 repetitions, primary care with 48 repetitions,

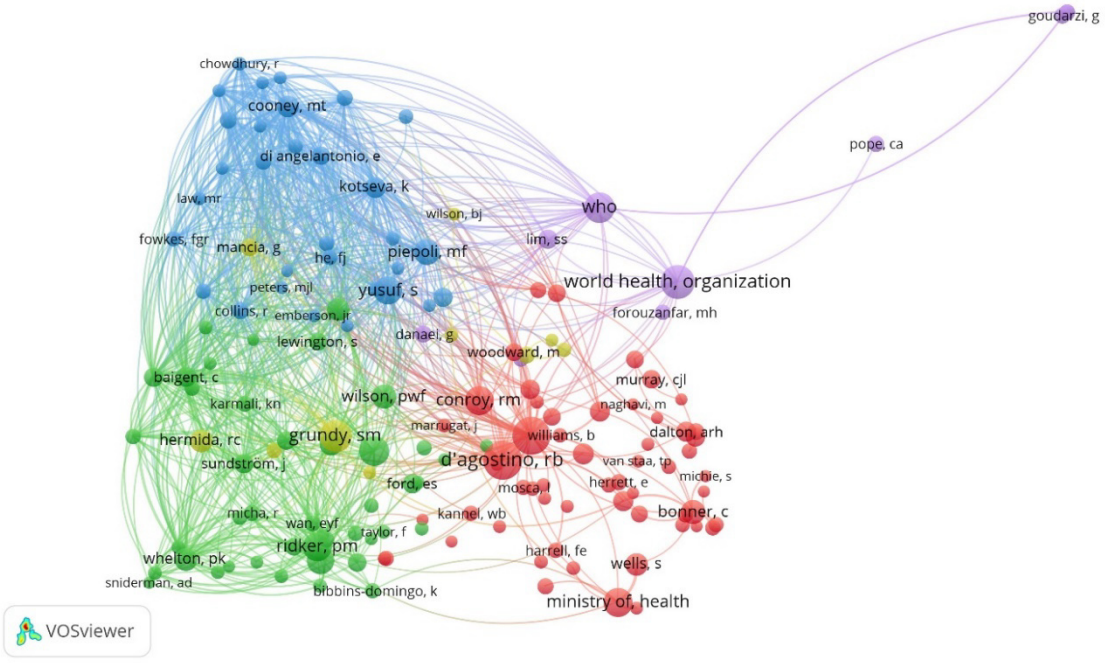


Fig. 7. **Co-citation of co-authors.**

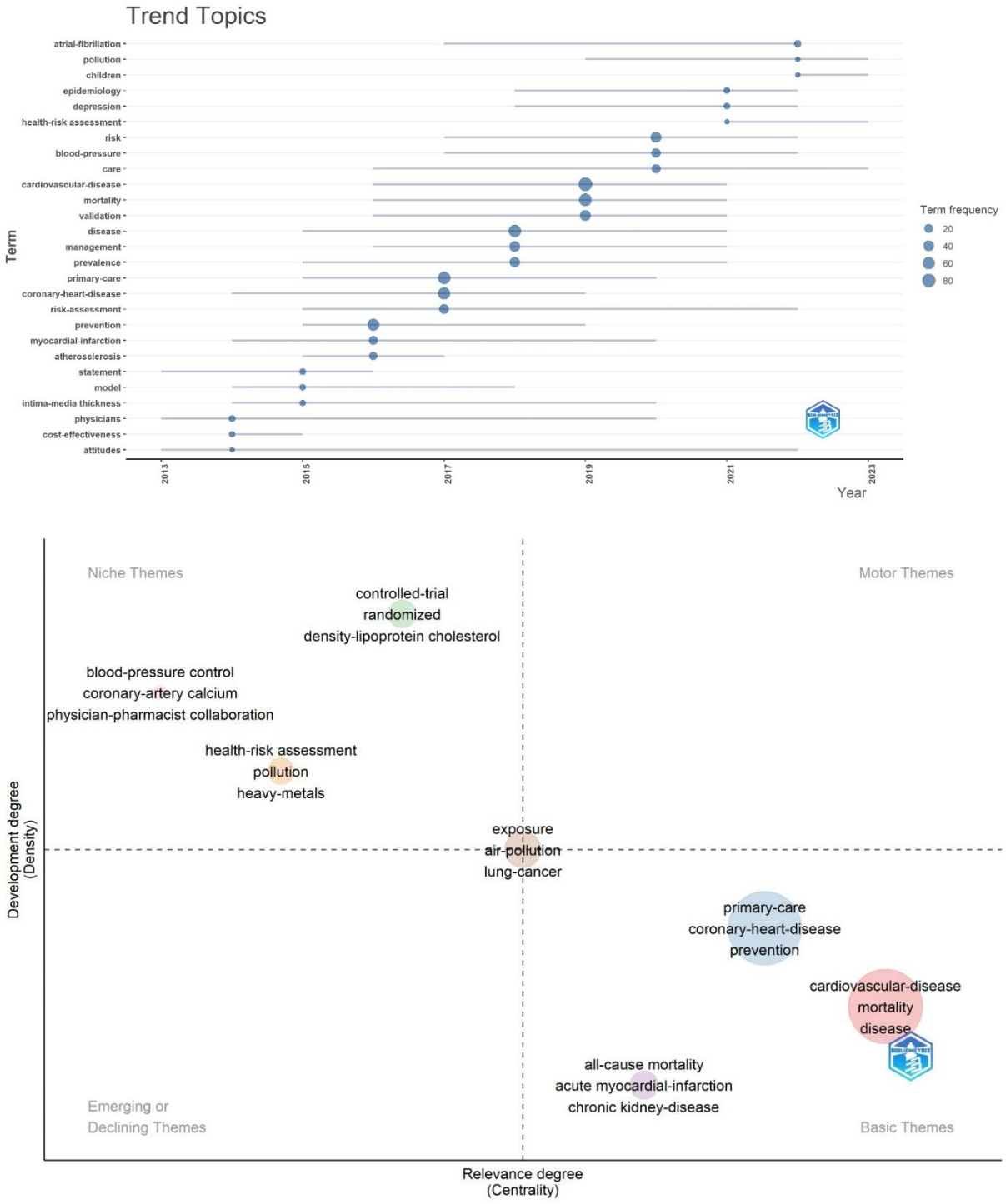


Fig. 8. Trending topics and thematic map.

and 42 repetitions. It contains the words hypertension and prevention with 37 repetitions. The strongest statements regarding total connection strength were risk assessment, cardiovascular disease, hypertension, blood pressure, and primary care. As a result of the analysis made with 143 observation units that were seen at least three times and had a relationship between them, a total of 5 clusters, 3024 connections, and 8482 total connection strength were detected (Fig. 6).

Co-citation of Co-authors

Different sources cited in a publication are called co-citation. According to the analysis performed on 152 units with the minimum number of citations se-

lected as 10, a total of 5 clusters, 5322 links and 33389 total link strength were detected. The most commonly cited authors were identified as D'agostino (96), Hippisley-cox (92) and World Health Organization (73) (Fig. 7).

Trending Topics and Thematic Map

Fig. 8 presents the worldwide trend topics of studies on the subject by year. When we examined the trend topics of the last year, “children”, " atrial-fibrillation" and " pollution" were global trends. The topics "blood-pressure control," “coronary-artery calcium,” “physician-pharmacist collaboration,” “density-lipoprotein cholesterol,” “randomized,” “health-risk assessment,” “pollution,” “heavy-metals" were niche themes that did not have a widespread impact. Not much work has been done on the topics in niche themes. There is potential here and researchers may want to evaluate this potential. The basic themes were " primary-care, coronary-heart-disease, prevention, cardiovascular-disease, mortality, disease." These themes were central, but the number of publications was still low (Fig. 8).

DISCUSSION

In this study, bibliometric analysis of 443 studies published on cardiovascular disease risk determination and prevention in primary care was performed using the VOSviewer program, and important publications, influential authors, authors' affiliations, leading countries and current trends regarding CVD risk assessment in primary care were determined. The unique value of this study is that there is no study in the literature that identifies the trends of studies on cardiovascular disease risk identification and prevention in primary care and visualizes countries, author collaborations, and citation networks. It is thought that this study will provide important information about the management of heart diseases in primary care and will make the current trends clear and understandable.

According to the analysis, it is seen that there has been an increase in the studies on determining and preventing the risk of cardiovascular disease in primary care in the last five years. However, it varies from year to year. The increasing number of publications in this field in recent years shows that the literature is deepening and expanding. According to WHO, more than four of the deaths caused by CVD, which is the leading cause of death in the world, are caused by heart attack and stroke [1]. Additionally, CVDs not only contribute significantly to the rising healthcare costs but also impose a high socio-economic burden on the general population. The review by Flora and Nayak emphasized that CVDs also create a high socio-economic burden on the general population [22]. Determining the risk of a heart attack is crucial as it can help in reducing the chances of deaths by up to 80%. Early risk-specific measures can be taken to prevent heart attacks, which can significantly reduce the socioeconomic burden on the general population. This highlights the importance of increasing research and developing strategies to combat cardiovascular diseases.

When we look at the partnership and citation analysis of the authors who contributed to the studies, it is seen that the number of citations and the link status do not show parallelism. Co-authorship is when two or more authors share their talents and resources by adopting one of the collaborative methods and collaborating to create a scientific work. One of the methods used to investigate co-authorship collaborations is an analysis of co-authorship networks [23]. Therefore, it is seen that there is a different process than the number of citations of authors. In this study, the most cited authors (Roger S. Blumenthal, Erin D. Michos, and Michelle A. Albert) and the most connected authors (Rod Jackson, Sue Wells, and Andrew Kerr) differ.
Studies on determining and preventing cardiovascular disease risk in primary care were carried out by authors from 64 different countries, and the most publications were made in the USA, England and Australia, respectively. According to the American Heart Association (AHA) in the United States, CVD tops the disease burden list, and projections show that by 2035, 45% of the U.S. adult population will be diagnosed with cardiovascular disease, costing more than $1 trillion annually [24]. It has been observed that cardiovascular diseases are a leading cause of premature deaths, accounting for one in four such deaths in the UK. Similarly, in Australia, these diseases cause about a quarter of the disease burden and two-thirds of all deaths. This highlights the severity of the situation [25]. The rising prevalence of CVD across the world, particularly in developed countries, has resulted in a high disease burden that is costly. However, research

shows that about 85% of CVD cases can be prevented if primary care is given priority. This highlights the importance of continued research in this field.

Although there are 997 different institutions contributing to the research studies, universities are the top contributors. The universities with the most citations are The University of North Carolina, North Western University, and Johns Hopkins University, respectively. However, the universities with the most publications vary depending on the countries in which they are located. Auckland University (31 publications), Cambridge University (15 publications), and Sydney University are among the top universities with the most publications. It is observed that the countries that produce the most publications are the USA, Australia, and England.

Upon examining the most cited publications, it is evident that the top 10 publications were published between 2015 and 2019. These studies are primarily focused on CVD prevention and evaluation and have been carried out by extensive research teams over multiple years of work. These studies have significantly contributed to the field and have led the way in this area. Among these studies, the guidelines published by two leading associations, AHA and the European Society of Cardiology, are of utmost importance [9, 26]. The increase in the number of citations can be attributed to the use of high-evidence recommendations and practices in studies pertaining to the identification and prevention of cardiovascular disease risk in primary care. These guidelines also provide guidance for planned studies.

Topics such as "blood-pressure control," "coronary-artery calcium," "physician-pharmacist collaboration," "density-lipoprotein cholesterol," "randomized," "health-risk assessment," "pollution," "heavy-metals" constitute the trending topics that need to be focused on in this field. When we look at the topics, it can be stated that the basic CVD risk factors, such as hypertension, high cholesterol, and atherosclerosis, are still not adequately addressed and that future research is needed in this field. Another notable trending topic is the increasing air pollution due to the effects of global warming. Air pollution and heavy metals can increase the risk of cardiovascular diseases (CVD) by causing hardening and inflammation of the arteries [27]. Therefore, it is essential to consider these factors in primary healthcare. Wang, Lin *et al*. conducted a bibliometric analysis and concluded that the literature includes studies on complications of cardiovascular risk, risk factors, and pharmacological prevention strategies [28]. The findings align with the results of this study. Additionally, the significance of pharmacological prevention strategies for CVD risk supports the trending topic of "physician-pharmacist collaboration" in our study.

The risk assessment conducted by researchers in randomized controlled studies, with a high level of evidence, and in planning studies that address risk factors such as hypertension, high cholesterol, air pollution, and heavy metals that cause atherosclerosis, will make significant contributions to the field. Collaborating with primary healthcare providers and policymakers to plan primary healthcare policies can help fill the gap in the field.

In publications related to determining and preventing the risk of cardiovascular disease in primary care, the most frequently used keywords are risk assessment, cardiovascular disease, primary care, hypertension, and prevention. This indicates that researchers working on this topic are primarily focused on identifying the risk of cardiovascular disease in primary care settings and the risk factors associated with it, including hypertension, dyslipidemia, diabetes, and smoking. The practices are based on guidelines and the main focus is on risk assessment and prevention.
It is worth noting that the WHO ranks among the top three co-cited organizations in publications related to determining and preventing cardiovascular disease risk in primary care. This is mainly due to the valuable resources that WHO offers, including prevalence and incidence data published on its website, high-evidence recommendations, and guidelines created by large working groups, which many authors frequently use.

Limitations

The first limitation of the research is that it only includes studies on identifying and preventing cardiovascular disease (CVD) risk that have been published in journals indexed in the "Web of Science Core Collection" database. The bibliometric analysis did not include any relevant studies published in non-indexed journals. The second limitation of the research is that the research only considered studies published in English, which may have excluded relevant studies published in other languages.

CONCLUSION

This bibliometric analysis examined the current state of research on identifying and preventing cardiovascular disease risk in primary care. The study identified the top contributing authors, institutions, collaborations, and trends in the field, finding that interest in this area has increased in recent years. The analysis showed that most studies focused on keywords such as "risk assessment," "cardiovascular disease," "primary care," "hypertension," and "prevention." If researchers focus on trending topics in future research like "blood-pressure control," "coronary-artery calcium," "physician-pharmacist collaboration," "low-density lipoprotein cholesterol," "health-risk assessment," "pollution," "primary care," "coronary heart disease," "prevention," "cardiovascular disease," and "mortality," it will help address the existing gap in the field. This area continues to be an active area of study for researchers. This bibliometric analysis has shown that guidelines published in the field of cardiovascular disease risk in primary care are crucial resources. Risk factors are also of great importance, and studies in this field require long-term global collaborations. Developed countries with a high disease burden are leading the field. Therefore, it is believed that addressing more risk factors, focusing on less addressed issues, and increasing global cooperation in studies planned in this field will contribute to expanding international literature in this area.

Authors' Contribution

Study Conception: ADA; Study Design: ADA; Supervision: ADA; Funding: ADA; Materials: ADA; Data Collection and/or Processing: ADA; Statistical Analysis and/or Data Interpretation: ADA; Literature Review: ADA; Manuscript Preparation: ADA and Critical Review: ADA.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. World Health Organization. Cardiovascular diseases 2024 [cited 2024 February 9]. Available from: https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1.
2. Roth GA, Mensah GA, Johnson CO, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.
3. Joseph P, Leong D, McKee M, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. Circ Res. 2017;121(6):677-694. doi: 10.1161/CIRCRESAHA.117.308903.
4. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. Geneva: World Health Organization press; 2007.
5. Otgontuya D, Oum S, Palam E, Rani M, Buckley BS. Individual-based primary prevention of cardiovascular disease in Cambodia and Mongolia: early identification and management of hypertension and diabetes mellitus. BMC Public Health. 2012;12:254. doi: 10.1186/1471-2458-12-254.
6. Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ. 2016;353:i2416. doi: 10.1136/bmj.i2416.
7. Lloyd-Jones DM, Wilson PW, Larson MG, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol. 2004;94(1):20-24. doi: 10.1016/j.amjcard.2004.03.023.
8. Conroy RM, Pyörälä K, Fitzgerald AP, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003. doi: 10.1016/s0195-668x(03)00114-3.
9. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016 Sep;252:207-274. doi: 10.1016/j.atherosclerosis.2016.05.037.
10. Mosca L, Benjamin EJ, Berra K, et al; American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol. 2011;57(12):1404-1423. doi: 10.1016/j.jacc.2011.02.005.
11. Perk J, De Backer G, Gohlke H, et al; Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice; European Association for Cardiovascular Prevention and Rehabilitation. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by represen-

tatives of nine societies and by invited experts). Atherosclerosis. 2012;223(1):1-68. doi: 10.1016/j.atherosclerosis.2012.05.007.
12. ESC Kılavuzları. Avrupa Klinik Uygulamada Kardiyovasküler Hastal›klardan Korunma K›lavuzu: Özet. Türk Kardiyol Dern Ars.2008;Suppl 1:153-192
13. Maroney K, Laurent J, Alvarado F, et al. Systematic review and meta-analysis of church-based interventions to improve cardiovascular disease risk factors. Am J Med Sci. 2023;366(3):199-208. doi: 10.1016/j.amjms.2023.05.010.
14. Gaziano TA. Reducing the growing burden of cardiovascular disease in the developing world. Health Aff (Millwood). 2007;26(1):13-24. doi: 10.1377/hlthaff.26.1.13.
15. Pennant M, Davenport C, Bayliss S, Greenheld W, Marshall T, Hyde C. Community programs for the prevention of cardiovascular disease: a systematic review. Am J Epidemiol. 2010;172(5):501-516. doi: 10.1093/aje/kwq171.
16. Soltani S, Saraf-Bank S, Basirat R, et al. Community-based cardiovascular disease prevention programmes and cardiovascular risk factors: a systematic review and meta-analysis. Public Health. 2021;200:59-70. doi: 10.1016/j.puhe.2021.09.006.
17. Erhan T, Dirik D, Eryilmaz İ. [A Bibliometric Analysis using VOSviewer of Publications on Post-Truth]. Sosyal Mucit Academic Review. 2023;4(2):164-88. doi: 10.54733/smar.1271369 [Article in Turkish]
18. Donthu N, Kumar S, Pandey N, Lim W. (2021). Research Constituents, Intellectual Structure, and Collaboration Patterns in Journal of International Marketing: An Analytical Retrospective. J Int Market. 2021;29(2):1-25. doi: 10.1177/1069031X211004234.
19. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: An overview and guidelines. J Bus Res. 2021;133:285-296. doi: 10.1016/j.jbusres.2021.04.070.
20. Eck NJv, Waltman L. VOSviewer Manual. 2023.
21. Aria M, Cuccurullo C. bibliometrix: An R-tool for comprehensive science mapping analysis. J Informetrics. 2017;11(4):959-975. doi: 10.1016/j.joi.2017.08.007
22. Flora GD, Nayak MK. A Brief Review of Cardiovascular Diseases, Associated Risk Factors and Current Treatment Regimes. Curr Pharm Des. 2019;25(38):4063-4084. doi: 10.2174/1381612825666190925163827.
23. Kumar S. Ethical Concerns in the Rise of Co-Authorship and Its Role as a Proxy of Research Collaborations. Publications. 2018;6(3):37. doi: 10.3390/publications6030037
24. American Heart Association (AHA). CDC Prevention Programs 2024 [cited 2024 March 12]. Available from: https://www.heart.org/en/get-involved/advocate/federal-priorities/cdc-prevention-programs.
25. Health AIo, Welfare. Prevention of cardiovascular disease, diabetes and chronic kidney disease: targeting risk factors. Canberra: AIHW; 2009
26. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646. doi: 10.1161/CIR.0000000000000678.
27. Zhang K, Brook RD, Li Y, Rajagopalan S, Kim JB. Air Pollution, Built Environment, and Early Cardiovascular Disease. Circ Res. 2023;132(12):1707-1724. doi: 10.1161/CIRCRESAHA.123.322002.
28. Wang L, Wang S, Song C, et al. Bibliometric analysis of residual cardiovascular risk: trends and frontiers. J Health Popul Nutr. 2023;42(1):132. doi: 10.1186/s41043-023-00478-z.
29. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1923-1994. doi: 10.1016/S0140-6736(18)32225-6.
30. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287-323. doi: 10.1016/S0140-6736(15)00128-2.
31. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. JAMA. 2017;317(9):912-924. doi: 10.1001/jama.2017.0947.

The European Research Journal 2024;10(6):588-599 Original Article

DOI: https://doi.org/10.18621/eurj.1448013 *Rheumatology*

Rheumatology nurses' knowledge and practices on pain management

Seda Pehlivan[1], Serap Özer[2]

[1]Department of Medical Nursing, Bursa Uludağ University, Faculty of Health Sciences, Bursa, Türkiye; [2]Department of Medical Nursing, Ege University, Faculty of Nursing, İzmir, Türkiye

ABSTRACT

Objectives: Nurses have important responsibilities in providing effective pain management. This study was conducted to determine the level of knowledge and practices of rheumatology nurses regarding pain management.

Methods: A descriptive study sample was 64 nurses in the rheumatology clinic. Data were collected using the Nurse Introduction Form and Questionnaire on Knowledge and Practices Regarding Pain Management. The data were evaluated in the SPSS.

Results: It was determined that 73.4% of the rheumatology nurses did not receive training on pain management. The pain management knowledge score was moderate, and the knowledge of non-pharmacological pain management was insufficient. The mean pain management self-confidence score was 6.03±2.01 (0-10), and a positive correlation was found between the graduation year, working years in rheumatology, and pain management knowledge score ($P<0.05$). Findings showed that the rheumatology nurses wanted to receive training on non-pharmacological interventions in pain management, pain-related psychosocial issues, and pain diagnosis.

Conclusion: Most of the participating rheumatology nurses did not receive training on pain management; their knowledge was only moderate, and they wanted to receive more training. As nurses' working years increased, the pain management self-confidence score increased. It is important to ensure orientation in the clinic by providing training to nurses who start to work in the rheumatology clinic regarding management and non-pharmacological interventions.

Keywords: Nursing, pain management, rheumatology

Pain is a universal human experience: it appears in many different dimensions, including the physical, mental, emotional, spiritual, existential, and interpersonal [1, 2]. The definition of pain The International Association for the Study of Pain (IASP) states, "Pain is a specific, unpleasant emotional experience with or without an organic cause, originating from any part of the body and including all past experiences of a person." [3]. Pain is classified as acute, chronic, and recurrent based on its duration. Chronic pain is defined as pain that continues longer than three months, longer than expected, or persists after recovery [4]. While chronic musculoskeletal pain is seen in 26-50% of adults, chronic low back pain may occur in 50-80% of the population at some time in their lives [5, 6]. However, pain is the predominant

Corresponding author: Seda Pehlivan, RN, PhD., Assoc Prof., Phone: +90 224 294 24 62, E-mail: pehlivan_seda@hotmail.com

How to cite this article: Pehlivan S, Özer S. Rheumatology nurses' knowledge and practices on pain management. Eur Res J. 2024;10(6):588-599. doi: 10.18621/eurj.1448013

Received: March 6, 2024
Accepted: April 3, 2024
Published Online: .May 21, 2024

symptom in most rheumatological diseases and is the primary reason for hospital admission for patients with inflammatory arthritis [7]. 68-88% of rheumatoid arthritis (RA) patients consider pain one of their top three priorities [8]. Chronic pain is very common in rheumatological diseases, where it starts for an etiological reason; it becomes the primary problem when recovery fails, resulting in immitigable pain associated with poor quality of life and an increased socioeconomic burden [4, 9].

Pain is the most common symptom in rheumatology patients: it negatively affects patients' daily activities and reduces their quality of life. Therefore, pain management of rheumatology patients is very important. Nurses should play an active role in the pain management of individuals with arthritis and regularly renew their knowledge of pain management methods [10]. Nurses must successfully manage pain to provide safe, quality, and recovery-supporting care. The nurse should provide the most appropriate individualized pain management by addressing the patient who is experiencing pain with a holistic approach. Sufficient pain management is already considered an international human right [1]. Therefore, all health professionals should have the necessary knowledge and skills to help rheumatology patients manage their pain better [7]. The American Pain Association defined pain as the "fifth vital sign" in 2010 [11]. Pain management in rheumatology patients includes assessment of pain (severity, type, duration), definition of the causes of pain (inflammatory, degenerative, widespread body pain), determination of the aims/expectations of treatment, development and implementation of the treatment plan, pharmacological treatments (treatment of disease and pain treatment), non-pharmacological treatments, assessment of the efficiency of treatment, physical activities and exercise, and patient education (joint protection, weight control, non-pharmacological practices) [7, 11]. Uncontrolled pain in rheumatology patients causes negative outcomes that include limitations in activities of daily life, limited resting activities, decreased socialization, anxiety, depression, sleep disorders, loss of appetite, and increased health service use and costs, thereby negatively affecting the quality of life [10]. When effective pain management is achieved in rheumatology patients, pain can be reduced, functionality and well-being can be increased, and individual and social costs (such as disability, increase in the number of days absent from work, recurrent hospital admissions, and hospitalizations) can be reduced [7]. Therefore, nurses in rheumatology cases should take responsibility regarding pain management to increase patients' quality of life.

Nurse-led pain management is a way to improve the provision of health service: nurses have key roles in pain management [4]. The global role of nurses in pain management is to provide pain management in accordance with the individual and cultural characteristics of the patient [1]. Nurses should have the necessary knowledge and skills for effective pain management; however, there are only a limited number of studies that evaluate the knowledge and practices of rheumatology nurses on pain management. In the study, found that rheumatology nurses defined pain as one of the distressful symptoms, and that they did not feel competent in pain management due to lack of information [12]. Some studies have been conducted with nurses in Turkey [13, 14, 15]; however, no study was found on pain management by rheumatology nurses. Studies conducted found that nurses have insufficient knowledge about pain management, pain diagnosis, and recommendations for reducing pain, and pharmacological treatment [13, 14]. However, determining the fields where nurses' lack of knowledge and practices in pain management are inadequate and the obstacles encountered is important in terms of planning the solution to the problems. Accordingly, the aim of our study was to determine the knowledge and practices of rheumatology nurses on pain management.

METHODS

In the present research, 64 nurses (28 via e-mail and 36 via face-to-face interviews) who were members of the Turkish Rheumatology Nurses Society, were employed in a rheumatology clinic, and volunteered to participate were included. Nurses who were employed in other clinics despite being a member of the society, who could not be reached at the time (October 2015-December 2016) of the study, and who did not complete the questionnaire were excluded from the study.

National Rheumatology Nurses Association of our

country was established in 2006 under the leadership of rheumatology nurses. The association, which had 87 registered members at the time of the research, continues its activities with 99 active members today. In the sample calculation of the study, the sample size was found to be 61 with α=0.05 and 0.95 confidence level (1-β). In post hoc power analysis; it was concluded that according to this effect size value, it reached 90% (0.8955774) power at the 95% confidence level and the sample size was sufficient.

Data Collection

The research data were collected using the Nurse Introduction Form and Questionnaire on Knowledge and Practices Regarding Pain Management. The questionnaire forms were sent to the e-mails (n=87) of the members of the national Rheumatology Nurses Society. After the rheumatology nurses filled out the questionnaire, it was sent to the researcher via e-mail (n=26). The security of the returned e-mails was checked. Since there was not enough feedback by mail, questionnaires were applied face-to-face by going to the clinics in the cities where the researchers lived. A total of 38 rheumatology nurses who were members of the association from 8 clinics were reached.

Nurse Introduction Form

The form consists of six questions regarding age, gender, educational status, marital status, graduation year, and years working as a rheumatology nurse.

Questionnaire on Knowledge and Practices Regarding Pain Management

The researchers created the questionnaire by reviewing the literature to determine nurses' knowledge and practices concerning patients having pain and the management of pain [15, 16]. The questionnaire form consists of 5 parts, having a total of 22 questions.

1. Causes of Pain

The most common causes of pain in rheumatological diseases were listed, and nurses were asked to indicate how often they encountered these conditions in clinical practice. The causes of pain in patients were grouped as “inflammatory joint pain (RA, PsA, etc.)”, “non-inflammatory joint pain (Osteoarthritis, trauma, etc.)”, “inflammatory back pain (SpA, AS, etc.)”, “non-inflammatory back pain (mechanical pain, etc.)” and “widespread body pain (Fibromyalgia, etc.)”. Nurses were asked to describe their encounter frequency as "rarely, “middle,” or often.”

2. The Status of Knowledge Regarding Pain Management

This part assessed the level of knowledge regarding pain management. Nurses were asked whether they had received pain management education. Eleven items about pain management were listed to determine nurses' knowledge of pain management. Nurses were asked to mark the given information as “true” or “false”. The score on knowledge regarding pain management was determined by awarding each correct item 1 score point (0-11).

3. The Practices Regarding Pain Management

In this section, there are questions to determine the practices used by nurses in pain management. It included questions about diagnosing pain, using a scale to assess pain, and pain-related record keeping. In addition, nurses were asked to evaluate their self-confidence in pain management with a 10-cm visual analogue scale (VAS). The self-confidence score was scored from 0=never to 10=always.

4. The Problems Related to Pain Management

This section has questions to determine the problems experienced (barriers, ethical dilemmas, subjects with educational needs) in pain management.

5. The Non-pharmacological Practices

In this section, the non-pharmacological methods used by nurses in pain management were asked. Nurses were asked about their knowledge and opinions about non-pharmacological practices (exercise, hot application, cold application, massage, aromatherapy, acupressure, acupuncture, yoga, meditation, reiki, music, other). For each non-pharmacological method, they were asked to mark the appropriate options among the options “I consider it beneficial”, “I recommend it to my patients”, and “I have no idea”.
The nurses completed the questionnaires in approximately 15-20 minutes.

Ethical Consideration

Ethical approval was obtained from the Scientific

Ethical Committee of Ege University Faculty of Nursing (Date: 30.09.2015, numbered 2015-113). Moreover, informed consent was requested from the Chairman of the Turkish Rheumatology Nurses Society and the participants who involved in this study. For all research, this must include a final section including details of ethical approval, informed consent, and, where relevant, registration.

Statistical Analysis

The data were evaluated using the Statistical Package for the Social Sciences (SPSS) and percentage, mean±standard deviation, and Pearson correlation analyses. A P-value of <0.05 was considered significant.

RESULTS

Sociodemographic Characteristics of Rheumatology Nurses

Considering the distribution of sociodemographic characteristics of rheumatology nurses, the mean age of the nurses was 34.68±7.05 years, and most of them had a bachelor's degree and were married. The mean time since graduation was 13.43±7.87 years, and the mean of working years in the rheumatology clinic was 6.42±5.91 years (Table 1).

Knowledge and Practices Regarding Pain Management

1. Causes of Pain

Table 2 shows data by frequency of encountering painful patients according to the reasons described by rheumatology nurses. Rheumatology nurses reported that the most common causes of pain were inflammatory joint pain (87.5%) and inflammatory back pain (51.5%). Non-inflammatory back pain and non-inflammatory joint pain were encountered less frequently than the other pain types.

2. The Status of Knowledge Regarding Pain Management

The majority of rheumatology nurses reported that they did not receive training in pain management (Table 1). The answers given by the nurses to the 11 items prepared to determine the pain management information are shown in Table 3. Each correct answer was scored 1 point, and the mean pain management knowledge score was 7.67±2.74 (0-11). The three statements that the nurses answered incorrectly were as follows: "Rheumatology patients' pain cannot be treated with non-pharmacological methods" "Pain should be treated when it reaches the level that the patient cannot tolerate any longer", and "Nurses can apply non-pharmacological methods independently in pain management". No correlation was found between the knowledge score and graduation time (r=0.061, P=0.631) and working years in rheumatology (r=0.061, P=0.633).

3. The Pain Management Practices

Table 4 shows the distribution of rheumatology nurses' pain management practices. The majority of the rheumatology nurses' did pain assessment regularly and used a scale for pain assessment. The majority of the nurses stated that they asked the patient how much pain he/she had while making a pain assessment. Again, the majority of the nurses stated that they administered painkillers (analgesic drugs) as ordered by a physician and contacting the patient's physician about pain. The topics included reporting changes in pain (35), discussing increases in drug amount(s) (11), discussing drug/administration route changes (7), and

Table 1. Descriptive characteristics of nurses

Characteristics	n (%) or (mean±SD)
Age (years)	34.68±7.05
Educational status	
Associate's degree	4 (6.3)
Bachelor's degree	56 (87.4)
Master's degree	4 (6.3)
Marital status	
Married	36 (56.2)
Single	28 (43.8)
Graduation time, *years*	13.43±7.87
Duration of working in rheumatology, *years*	6.42±5.91
Education of pain management	
Yes	17 (26.6)
No	47 (73.4)

Table 2. Frequency of nurses encountering painful patients by reasons

Causes of pain	Encounter Frequency					
	Rarely		Middle		Often	
	n	%	n	%	n	%
Inflammatory joint pain (RA, PsA, etc)	2	3.1	6	9.4	56	87.5
Non-inflammatory joint pain (Osteoarthritis, trauma, etc)	13	20.3	24	37.5	27	42.2
Inflammatory back pain (SpA, AS, etc)	4	6.3	27	42.2	33	51.5
Non-inflammatory back pain (Mechanical pain, etc)	18	28.1	31	48.4	15	23.5
Widespread body pain (Fibromyaljia, etc)	10	15.6	32	50.0	22	34.4

RA=rheumatoid arthritis, PsA=psoriatic arthritis, SpA=spondylarthritis, As=ankylosing spondylitis

reporting drug side effects (1). The majority of nurses reported that they kept records about pain and entered the records on the nurse observation form. Nurses reported that they most frequently needed to decide on "the identification of pain and its severity," and "the drugs and administration time". The mean pain management self-confidence score of the rheumatology nurses was 6.03±2.01 (0–10). A positive correlation was found between the self-confidence score and the graduation year (r=0.268, P=0.038), working years in rheumatology (r=0.296, P=0.018), and pain management knowledge score (r=0.334, P=0.007).

4. The Problems Related to Pain Management

Twenty-eight (43.8%) rheumatology nurses answered "yes" to the question of whether they encountered any barriers in relieving the pain. These barriers included insufficient drug ordering (10), lack of patient cooperation (9), lack of patient/family knowledge (7), insufficient time (4), and insufficient physician cooperation (3). The three most important issues with professional ethical dilemmas in pain management were problems or anxiety about administering too many drugs (50.0%), feeling that the pain could not be relieved sufficiently (46.8%), and conflict with the physician (35.9%). Considering the distribution of the subjects that required training on pain management, it was found that the top three subjects were non-pharmacological interventions, psychosocial issues related to pain, and pain diagnosis (Table 5).

Table 3. Knowledge of pain and pain management

Pain and pain management related items	Knowing		Unknowing	
	n	%	n	%
Pain is a multidimensional experience and the one who best experienced it can describe it. (T)	56	87.5	8	12.5
Pain can cause many problems such as loss of appetite and insomnia. (T)	58	90.6	6	9.4
When the pain reaches the level that the patient cannot bear, it should be treated. (F)	25	39.1	39	60.9
Pain treatment should always be individualized. (T)	53	82.8	11	17.2
Patients can live painlessly with appropriate treatment. (T)	54	84.4	10	15.6
It is natural for the patient to wait for the pain to pass completely after the treatment. (T)	48	75.0	16	25.0
There are non-pharmacological pain treatment methods that can be recommended to rheumatology patients. (T)	45	70.3	19	29.7
The pain of rheumatology patients cannot be treated with non-pharmacological methods. (F)	14	21.8	50	78.2
Nurses can independently apply non-pharmacological methods in pain management. (T)	38	59.4	26	40.6
Nurses can recommend non-pharmacological pain treatment methods to their patients. (T)	41	64.1	23	35.9
Nurses have an important place in the multidisciplinary pain management team. (T)	52	81.3	12	18.7

T=True, F=False

Table 4. Nurses' practices on pain management

Practices	n	%
Regular pain assessment		
No	54	84.4
Yes	10	15.6
Using a scale in pain assessment		
Yes	54	84.4
No	10	15.6
When assessing pain		
I observe the patient's behavior.	15	23.4
I ask the patient how much pain he has.	41	64.1
I review the physician notes	0	0
I evaluate the verbal information given by my nurse colleagues.	1	1.6
All	7	10.9
When administering analgesic drugs		
I give it less often than ordered.	5	7.8
I give it more often than is ordered.	0	0
I give drugs other than analgesic drugs (antiemetic, sedative, etc.)	2	3.1
I give it as ordered.	57	89.1
Non-pharmacological method application in the clinic		
Yes	25	39.1
No	39	60.9
Contacting the doctor about pain		
Yes	54	84.4
No	10	15.6
Pain related record keeping		
Yes	57	89.1
No	7	10.9
Decision-making issue regarding pain		
Identifying the pain	10	15.6
Defining the severity of pain	34	53.2
Medicines	13	20.3
Time of drugs	7	10.9
Self-confidence in pain management (0-10) (mean±SD)	6.03±2.01	

5. The Non-pharmacological Practices

Twenty-five (39.1%) rheumatology nurses stated that non-pharmacological practices were performed in the clinic: cold application (14), physiotherapy (10), hot application (5), and exercise (1) (Multiple practices reported). Non-pharmacological methods that the nurses considered beneficial were exercise (73.4%), physiotherapy (64.1%), and massage (59.4%). The non-pharmacological methods they recommended were cold application (17.2%), massage (17.2%,) and

Table 5. The problems experienced by nurses in pain management

Problems	n	%
Barriers in relieving the pain		
Yes	28	43.8
No	36	56.3
The most important professional ethical dilemmas in pain management*		
Worry about giving too much medication	32	50.0
Concern about giving small amounts of medication	16	25.0
Feeling that the patient cannot adequately relieve pain	30	46.8
Worry about addiction	18	28.1
Concern about respiratory depression	21	32.8
Knowing that the patient has pain and not accepting it	8	12.5
Don't doubt that the pain is real	16	25.0
Conflict with the doctor	23	35.9
Conflict with patient and family	21	32.8
The subjects that required training on pain management		
Pain diagnosis	34	53.1
Pharmacological management of pain	33	51.5
Analgesia pumps	23	35.9
Nonpharmacological interventions	40	62.5
Psychosocial issues related to pain	38	59.3
Pain management in special populations	18	28.1

*More than one option is marked.

Table 6. The non-pharmacological practices

Nonpharmacological Practices	Beneficial		Recommend		No idea	
	n	%	n	%	n	%
Exercise	47	73.4	7	10.9	3	4.7
Hot application	28	43.8	10	15.6	13	20.3
Cold application	31	48.4	11	17.2	18	28.1
Massage	38	59.4	11	17.2	11	17.2
Physiotherapy	41	64.1	8	12.5	13	20.3
Herbal tharapy	12	18.8	4	6.3	40	62.5
Aromatherapy	14	21.9	2	3.1	45	70.3
Acupressure	11	17.2	2	3.1	50	78.1
Acupuncture	21	32.8	1	1.6	41	64.1
Yoga	22	34.4	5	7.8	36	56.3
Meditation	23	35.9	4	6.3	36	56.3
Reiki	14	21.9	2	3.1	47	73.4
Music	28	43.8	9	14.1	27	42.2

hot application (15.6%). The non-pharmacological methods that the nurses had no idea about were acupressure (78.1%), reiki (73.4%), and aromatherapy (70.3%) (Table 6).

DISCUSSION

The majority of the rheumatology nurses did not receive training on pain management: their knowledge was only at a moderate level, and they wanted to receive more training. As nurses' working years increased, the pain management self-confidence score increased. Pain is among patients' most frequently reported symptoms: approximately 79% of hospitalized patients experience pain [17]. Looking at the history of nursing; it seems to be a longstanding tradition of comforting the sufferers [18]. Nurses are the health service providers who are not only responsible for relieving patients' pain but also play an important role in managing patients' pain. However, many international organizations dealing with the improvement of the safety and quality of health of patients have addressed this problem and reported that nurses provide insufficient pain management in all countries. Furthermore, it has been emphasized that neglecting patients' pain is ethically and morally unacceptable [17]. The European League Against Rheumatism (EULAR) defined rheumatology nurses as the part of the health care team who make decisions along with patients and provide evidence-based care. Rheumatology nurses have several roles, including self-management support, patient education, person-to-person counselling, and even telephone counselling. The EULAR, on the other hand, emphasized that each patient needs to reach out to a nurse from whom they can receive education that will improve their disease management [19]. Patient education on pain management should include the causes of pain, pharmacological treatments and their side effects, non-pharmacological practices, self-help, physical activity, joint protection exercises, behavioral changes, and weight control [10, 20]. Parlar *et al*. [10], in a study of arthritis patients, found that those who received education on pain management experienced decreased pain severity, increased use of non-pharmacological interventions, and achieved positive impacts related to coping with pain and daily activities.

Causes of Pain

In the management of pain in rheumatological diseases, first of all, the etiology of pain should be determined. In rheumatological diseases, sources of pain can be divided into inflammatory, degenerative, and widespread body pain [7]. Rheumatology nurses reported that the causes of pain they encountered in patients were often inflammatory joint pain and inflammatory back pain, less frequently non-inflammatory back pain, and non-inflammatory joint pain. These results show that nurses encounter diseases such as RA and ankylosing spondylitis (AS) more frequently in clinics. To know if the pain is inflammatory is important in terms of determining the right applications (Hot application or thermal water should not be recommended for inflammatory pain).

The Status of Knowledge Regarding Pain Management

It is of vital importance to manage chronic musculoskeletal pain with effective, safe, and low-cost approaches [21]. Pain management is a primary issue in rheumatic diseases, and pain management should be at the center of training and research studies in rheumatology [11]. A study was conducted to identify the basic education issues and problems, and then to suggest solutions for rheumatology clinicians (nurses, physiotherapists, occupational therapists) and educators in undergraduate education for rheumatology practice. That study determined that the roles of nurses on pain management, administration and monitoring of analgesics; training and self-management of the patient should be included in the educational content of nurses [22]. Another study emphasized that nursing students' pain knowledge and attitude scores were low and that the nursing educators should make more efforts to improve pain education in the current curriculum and ensure nursing students develop pain management attitudes [23]. Demir Dikmen *et al*. [13] determined that nurses' knowledge and behavior scores about patients in pain and their pain management were at a moderate level; the authors concluded that most of the nurses did not have sufficient knowledge about pain diagnosis and management. In our study, most of the nurses reported that they did not receive training on pain management and that their pain management knowledge score was only at a moderate level. These findings are consistent with the literature.

For this reason, it is suggested that pain management should be included more often, both in the content of undergraduate education and in-service training programs after graduation.

Pharmacological treatment of pain may remain insufficient in terms of effectiveness, and it has been also reported to be associated with various toxicities [11]. Therefore, the authors emphasized that non-pharmacological pain treatment is an inseparable part of pain management [24]. This conclusion is supported by evidence from another study showing that the use of analgesics can be reduced without increasing pain by benefitting from non-pharmacological interventions more in pain management guided by nurses [4]. It should be also noted that patients are more willing to use these methods. Notably, several studies emphasized that nurses should provide training and counseling to their patients on non-pharmacological methods as well as pharmacological methods in pain management [24, 25]. Other studies determined that nurses initially treated patients in pain with analgesics [4, 14, 26, 27]. One study found that the reason why nurses used non-pharmacological interventions on a limited level in pain management was related to their inadequate education on pain management [28]. The results of recent systematic review and meta-analysis studies showed that non-pharmacological practices were effective in reducing the pain of rheumatology patients. Some of these practices were even included in the American College of Rheumatology (ACR) guidelines because of their high efficiency [11].

The level of pain experienced by the patients and patient care outcomes are affected by the knowledge, attitudes, and behaviors of the nurses providing their care. It was observed that the insufficiency of nurses' knowledge and experience is a cause of ineffective pain management [29]. In our study, a positive correlation was found between the pain management self-confidence score and the knowledge score, supporting that information. A previous study determined that rheumatology nurses mainly rely on informal sources of information (interactions with physicians and patients) and their professional experiences gained in the clinic over the years [30]. In our study, the pain management self-confidence score increased as the working years in the rheumatology clinic increased. This finding can be explained by the above-mentioned information. However, this learning method is time-consuming; therefore, formal evidence-based learning needs to be facilitated and expanded on pain management as an important issue. Accordingly, institutions and managers of rheumatology clinics also have major responsibilities. Pain management protocols should be developed by following the current evidence-based literature, and nurses should be encouraged to implement these protocols.

The Practices and Problems Related to Pain Management

Pain management practices are hindered by three main obstacles: patients' obstacles, organizational obstacles, and health service providers' obstacles. Nurses' knowledge of pain management is reported to be the strongest independent determinant of patients' pain management practices. Therefore, nurses are recommended to focus on their knowledge and attitudes on pain management to improve their practice in pain management [17]. Demir Dikmen *et al*. [13] found that 36.8% of the nurses encountered barriers to acquiring that knowledge. Ryan *et al*. [12] conducted a study with rheumatology nurses and determined that the most important barriers encountered in pain management were lack of time and lack of knowledge. In our study, approximately half of the nurses reported that they encountered obstacles in pain management, and that the barriers they encountered were mostly caused by external reasons (insufficient drug ordering, lack of patient cooperation, lack of patient/family knowledge, and insufficient physician cooperation). Moreover, the three most important issues with professional ethical dilemmas in pain management were found to be problems/anxiety about administering too many drugs (50.0%), feeling that the pain could not be relieved sufficiently (46.8%), and conflict with the physician (35.9%). The subjects requiring training on pain management were found as non-pharmacological interventions, psychosocial issues related to pain, and pain diagnosis. Demir Dikmen *et al*. [13] determined that the issues in which nurses had ethical dilemmas were fear of "administering overdoses" (36.5%) and "addiction" (30.6%), and that the subjects that required information were pain diagnosis (41.9%), pharmacological management of pain (27.6%), non-pharmacological interventions in pain manage-

ment (15.9%). These findings show that the ethical problems and training requirements of nurses on pain management are similar in all working environments.

The Non-pharmacological Practices

Non-pharmacological management of pain in rheumatology patients includes patient education, physical and occupational therapy, diet and weight control, physical activity, massage, yoga, meditation, aromatherapy, behavior therapies that include cognitive-behavioral therapy, and development of self-management strategies [11]. Rheumatology nurses can determine pain management-related non-pharmacological interventions appropriate for their patients, implement these interventions independently, and even teach them to their patients, implement the methods concurrently with them, and assess the results together [31, 32]. Nursing studies conducted with rheumatology patients showed that methods such as pain management training, exercise, massage, aromatherapy, reflexology, music, and yoga are some of the non-pharmacological methods that are effective in reducing pain [10, 33-38]. These results show that non-pharmacological interventions applied by nurses in pain management are simple, independently applicable, safe, and most importantly, effective [37]. In both previous studies and our study, nurses were determined to have insufficient knowledge about using non-pharmacological interventions and how to recommend them to the patients and that they want to receive training on this subject [13, 14, 26, 27]. The main reason of the lack of knowledge on non-pharmacological interventions may be because evidence-based practices are not included in nursing education and nurses are not informed about the study results. A study reported that the sources of information of rheumatology nurses included primarily colleagues and medical doctors and that research-based nursing knowledge and studies played a limited role [30]. To eliminate these deficiencies in rheumatology nurses' training on non-pharmacological methods, it is necessary to ensure nurses keep up with relevant studies, to inform nurses who have difficulties in keeping up about the study results, and to share information in appropriate learning environments. Additionally, nurses can be informed about the courses and certificate programs regarding non-pharmacological methods including aromatherapy, acupressure, and reiki which require special education, and their participation can be encouraged accordingly.

Limitations

Due to the low number of nurses who are members of the rheumatology nursing association and the low rate of answering the questionnaires, a limited number of nurses participated in the study, although the working period was extended. Giving together data obtained by different methods (e-mail and face-to-face) may be another limitation of the study

CONCLUSION

In our study, we found that most of the rheumatology nurses performed pain assessment; however, their pain management knowledge and self-confidence were only at moderate levels. It was seen that the most important deficiency in nurses' knowledge was about non-pharmacological interventions, and that they wanted to get information on this issue. Furthermore, it was important that the self-confidence in pain management increased as the working years in the clinic increased, indicating that pain management education should be more often included during undergraduate nursing education. The literature emphasizes the preparation of nursing students to analytically implement their pain knowledge and their acquiring positive pain attitudes is necessary for their future nursing roles [23]. Nursing education programs should also include evidence-based interventions regarding pain management. Despite all that, managers should consider that newly graduated nurses may have deficiencies on pain management. For this reason, comprehensive in-service training on pain management and evidence-based non-pharmacological interventions should be provided to nurses who will work in clinics such as rheumatology and the results of that training should be evaluated. Nurses should be encouraged to participate in activities such as conferences, symposiums, and courses to develop competencies on non-pharmacological practices (aromatherapy, massage, reiki, yoga, etc.). In addition, institutions and clinics can develop pain management protocols, and nurses can follow and implement these protocols.

Authors' Contribution

Study Conception: SP; Study Design: SP, SÖ; Supervision: SP, SÖ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SP; Statistical Analysis and/or Data Interpretation: SP; Literature Review: SP, SÖ; Manuscript Preparation: SP and Critical Review: SP, SÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgement

The authors thank all the rheumatology nurses who participated in the study.

REFERENCES

1. Rosa WE. Transcultural Pain Management: Theory, Practice, and Nurse-Client Partnerships. Pain Manag Nurs. 2018;19(1):23-33. doi: 10.1016/j.pmn.2017.10.007.
2. Özveren H, Faydalı S, Gülnar E, Dokuz HF. [Attitude and applications of nurses to evaluate pain]. J Contemp Med. 2018;8(1):60-66. doi: 10.16899/gopctd.388195. [Article in Turkish].
3. International Association for the Study of Pain (IASP) Terminology. (Last Updated: December 14, 2017). https://www.iasp-pain.org/terminology?navItemNumber=576#Pain. Accessed June 17, 2020.
4. Courtenay M, Carey N. The impact and effectiveness of nurse-led care in the management of acute and chronic pain: a review of the literature. J Clin Nurs. 2008;17(15):2001-2013. doi: 10.1111/j.1365-2702.2008.02361.x.
5. Köken İŞ, Eyigör C. [Interventional pain treatment modalities in palliation of rheumatic pains]. Ege Tıp Dergisi. 2019;58(Supp):22-26. doi: 10.19161/etd.648690. [Article in Turkish]
6. Rubin DI. Epidemiology and risk factors for spine pain. Neurol Clin. 2007;25(2):353-371. doi: 10.1016/j.ncl.2007.01.004.
7. Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018;77(6):797-807. doi: 10.1136/annrheumdis-2017-212662.
8. Lee YC. Effect and treatment of chronic pain in inflammatory arthritis. Curr Rheumatol Rep. 2013;15(1):300. doi: 10.1007/s11926-012-0300-4.
9. Akdemir N, Akyar İ, Görgülü Ü. [Nurses' approaches towards the pain problem of patients admitted to physical therapy and rehabilitation inpatient and outpatient clinics]. Turk J Phys Med Rehab. 2008;54(4):157-163. [Article in Turkish]
10. Parlar S, Fadiloglu C, Argon G, Tokem Y, Keser G. The effects of self-pain management on the intensity of pain and pain management methods in arthritic patients. Pain Manag Nurs. 2013;14(3):133-142. doi: 10.1016/j.pmn.2010.08.002.
11. Borenstein DG, Hassett AL, Pisetsky D. Pain management in rheumatology research, training, and practice. Clin Exp Rheumatol. 2017;35 Suppl 107(5):2-7.
12. Ryan S, McCabe CS, Adams J. The current knowledge and confidence of rheumatology nurses in providing advice on pain management. Musculoskeletal Care. 2016;14(1):62-66. doi: 10.1002/msc.1113.
13. Demir Dikmen Y, Usta Yıldırım Y, İnce Y, Türken Gel K, Akı Kaya M. [Determining of nurses' knowledge, behavior and clinical decision making regarding pain management]. Çağdaş Tıp Dergisi. 2012;2(3):162-172. [Article in Turkish]
14. Yılmaz M, Gürler H. [Nursing approaches toward postoperative pain in patients: patients' opinions]. Agri. 2011;23(2):71-79. doi: 10.5505/agri.2011.36349. [Article in Turkish]
15. Ozer S, Akyürek B, Başbakkal Z. [Investigation of nurses' pain related knowledge, attitude and clinical decision making skills]. Agri. 2006;18(4):36-43. [Article in Turkish]
16. Ferrell BR, Eberts MT, McCaffery M, Grant M. The Clinical Decision Making Survey (CDMS) Measurement Instrument Database for the Social Science. 2012. https://www.midss.org/sites/default/files/clinical_decision_making.pdf. Accessed December 19, 2019.
17. Alzghoul BI, Abdullah NA. Pain management practices by nurses: an application of the Knowledge, Attitude and Practices (KAP) Model. Glob J Health Sci. 2015;8(6):154-160. doi: 10.5539/gjhs.v8n6p154.
18. Wells-Federman C, Arnstein P, Caudill M. Nurse-led pain management program: effect on self-efficacy, pain intensity, pain-related disability, and depressive symptoms in chronic pain patients. Pain Manag Nurs. 2002;3(4):131-140. doi: 10.1053/jpmn.2002.127178.
19. Bech B, Primdahl J, van Tubergen A, et al. 2018 update of the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Ann Rheum Dis. 2020;79(1):61-68. doi: 10.1136/annrheumdis-2019-215458.
20. Zangi HA, Ndosi M, Adams J, et al; European League Against Rheumatism (EULAR). EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis. 2015;74(6):954-962. doi: 10.1136/annrheumdis-2014-206807.
21. Du S, Yuan C, Xiao X, Chu J, Qiu Y, Qian H. Self-management programs for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. Patient Educ Couns. 2011;85(3):e299-310. doi: 10.1016/j.pec.2011.02.021.
22. Hewlett S, Clarke B, O'Brien A, et al. Rheumatology education for undergraduate nursing, physiotherapy and occupational therapy students in the UK: standards, challenges and solutions. Rheumatology (Oxford). 2008;47(7):1025-1030. doi: 10.1093/rheumatology/ken139.

23. Chan JC, Hamamura T. Emotional intelligence, pain knowledge, and attitudes of nursing students in Hong Kong. Pain Manag Nurs. 2016;17(2):159-168. doi: 10.1016/j.pmn.2016.02.001.
24. Kalinowski S, Budnick A, Kuhnert R, et al. Nonpharmacologic Pain Management Interventions in German Nursing Homes: A Cluster Randomized Trial. Pain Manag Nurs. 2015;16(4):464-474. doi: 10.1016/j.pmn.2014.09.002.
25. Menefee LA, Monti DA. Nonpharmacologic and complementary approaches to cancer pain management. J Am Osteopath Assoc. 2005;105(11 Suppl 5):S15-20.
26. Göl İ, Onarıcı M. [Nurses' knowledge and practices about pain and pain control in children]. Hacettepe Üniversitesi Hemşirelik Fakültesi Dergisi.2015;2(3):20-29. [Article in Turkish]
27. Yılmaz F, Atay S. [Clinical pain management of nursing students]. Hacettepe Üniversitesi Hemşirelik Fakültesi Dergisi. 2014;1(2):32-41. [Article in Turkish]
28. Lewis MJM, Kohtz C, Emmerling S, Fisher M, Mcgarvey J. Pain control and nonpharmacologic interventions. Nursing. 2018;48(9):65-68. doi: 10.1097/01.NURSE.0000544231.59222.ab.
29. Akbaş M, Tosunöz İK. [Knowledge and approaches of nurses about pain related interventions]. Cukurova Med J 2019;44(1):136-143. doi: 10.17826/cumj.431892. [Article in Turkish]
30. Neher M, Ståhl C, Ellström PE, Nilsen P. Knowledge sources for evidence-based practice in rheumatology nursing. Clin Nurs Res. 2015;24(6):661-679. doi: 10.1177/1054773814543355.
31. Sağkal Midilli T, Eşer İ, Yücel Ş. [The use of nonpharmacological methods in pain management of nurses working in surgical clinics and factors affecting their use]. ACU Sağlık Bil Derg. 2019;10(1):60-66. doi: 10.31067/0.2018.72. [Article in Turkish]
32. Van Niekerk LM, Martin F. Tasmanian nurses' knowledge of pain management. Int J Nurs Stud. 2001;38(2):141-52. doi: 10.1016/s0020-7489(00)00053-5.
33. Lauche R, Hunter DJ, Adams J, Cramer H. Yoga for Osteoarthritis: a Systematic Review and Meta-analysis. Curr Rheumatol Rep. 2019;21(9):47. doi: 10.1007/s11926-019-0846-5.
34. Pehlivan S, Karadakovan A. Effects of aromatherapy massage on pain, functional state, and quality of life in an elderly individual with knee osteoarthritis. Jpn J Nurs Sci. 2019;16(4):450-458. doi: 10.1111/jjns.12254.
35. Bakir E, Baglama SS, Gursoy S. The effects of reflexology on pain and sleep deprivation in patients with rheumatoid arthritis: A randomized controlled trial. Complement Ther Clin Pract. 2018;31:315-319. doi: 10.1016/j.ctcp.2018.02.017.
36. Alparslan GB, Babadağ B, Özkaraman A, Yıldız P, Musmul A, Korkmaz C. Effects of music on pain in patients with fibromyalgia. Clin Rheumatol. 2016;35(5):1317-1321. doi: 10.1007/s10067-015-3046-3.
37. Gok Metin Z, Ozdemir L. The Effects of Aromatherapy Massage and Reflexology on Pain and Fatigue in Patients with Rheumatoid Arthritis: A Randomized Controlled Trial. Pain Manag Nurs. 2016;17(2):140-149. doi: 10.1016/j.pmn.2016.01.004.
38. Larsson A, Palstam A, Löfgren M, et al. Resistance exercise improves muscle strength, health status and pain intensity in fibromyalgia--a randomized controlled trial. Arthritis Res Ther. 2015;17(1):161. doi: 10.1186/s13075-015-0679-1.

The European Research Journal 2024;10(6):600-608 Original Article

DOI: https://doi.org/10.18621/eurj.1418269 *Orthopedics and Traumatology*

The economic impact of two-stage knee arthroplasty revisions: a projection for a specialized health center in Türkiye

Alparslan Yurtbay[1], Ahmet Ersoy[2], Cahit Şemsi Şay[3], Ferhat Say[3]

[1]Department of Orthopedics and Traumatology, Samsun University, Faculty of Medicine, Samsun, Türkiye, [2]Department of Orthopedics and Traumatology, Turhal State Hospital, Tokat, Türkiye, [3]Department of Orthopedics and Traumatology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Türkiye

ABSTRACT

Objectives: The increase in the number of arthroplasty surgeries worldwide also leads to an increase in revision surgeries. This study examines the costs of primary and revision arthroplasty treatments in a tertiary university hospital's orthopedics and traumatology clinic. It also explores the impact of revision surgeries on the healthcare system.

Methods: Seventy-six patients who had total knee arthroplasty at a university hospital between 01.01.2017 and 30.09.2022 were included in the study. The patients were divided into three groups: primary (n=25), aseptic reasons one-stage revision (n=27), and septic reasons two-stage revisions (n=24). For each patient included in the study, detailed documents regarding medical supplies, anesthesia, operating room, intensive care, consultation, medicine/serum, medical treatment, laboratory, blood and blood products, microbiology, radiology, food, bed, and attendant fees were provided separately by the hospital purchasing and statistics departments.

Results: When comparing the costs of primary, one-stage revision, and two-stage revision surgeries, the average costs were 5689 Turkish Lira (₺), 8294.97 ₺, and 40919.67 ₺, respectively. In patients with septic reasons, the group that underwent two-stage revisions had significantly higher costs than the aseptic group in terms of surgery time, hospital stay duration, medication, treatment, surgery, anesthesia, intensive care, laboratory tests, imaging, blood center services, consultations, visits, meal expenses, and invoiced amount (P<0.001).

Conclusion: Preventing and treating periprosthetic infections is costly and challenging. We need more research to develop effective protocols and reduce costs. As the number of patients undergoing knee arthroplasty is expected to rise, healthcare systems must ensure the sustainability of public financial resources, especially in public university hospitals.

Keywords: Arthroplasty, knee replacement, revision, cost analysis, hospital economics

Osteoarthritis continues to be an essential public health problem worldwide [1]. Due to the population's increasing age and expectations from daily life, the number of prosthetic joint replacement operations is increasing daily. Since the demand for joint arthroplasty is expected to increase significantly

Corresponding author: Alparslan Yurtbay, MD., Assist. Prof., Phone: +90 362 313 00 55, E-mail: yurtbayalparslan@gmail.com

How to cite this article: Yurtbay A, Ersoy A, Şay CŞ, Say F. The economic impact of two-stage knee arthroplasty revisions: a projection for a specialized health center in Türkiye. Eur Res J. 2024;10(6):600-608. doi: 10.18621/eurj.1418269

Received: January 11, 2024
Accepted: March 16, 2024
Published Online: May 10, 2024

in the coming years, it is natural to expect that the number of knee revisions and the economic burden of prosthetic infections will increase over the years [2]. In a study conducted in Germany, the number of geriatric patients is expected to increase in the coming years, and the use of orthopedic implants will increase rapidly. The same study predicted that the incidence of total knee arthroplasty (TKA) operations would increase by 43%, and a total of 225,957 TKA procedures will be applied in 2050. In addition, it is predicted that annual TKA revision operations will increase rapidly by 90% [3].

The increase in the elderly group and the number of applied prostheses increase the number of implant failures. The most common causes of implant failure and need for revision are instability, mechanical loosening, incorrect prosthesis positioning, dislocation, polyethylene wear, periprosthetic fractures, and infection [4]. Periprosthetic infection is a very devastating complication that increases the time and cost of treatment. The infection rate in knee arthroplasty ranges from 0,4% to 2% in primary total knee replacement and 5,6% in revisions [5]. Prosthetic joint infections (PJIs) have increased, as is obvious, and we anticipate that this trend will continue as more primary joints are replaced.

Two-stage revision is the most commonly used treatment method worldwide in treating infected hip and knee arthroplasty [6]. In the first stage, the infected prosthesis is removed. The local antibiotic release aims to fill the formed space with antibiotic bone cement (spacer). At the same time, systemic infection control is tried to be achieved with intravenous (IV) antibiotics. After infection control is ensured with antibiotics lasting an average of 4 months (2-6 months), the spacer is removed, and the final treatment is implant placement. During all this time, patients undergo a very costly treatment process, considering prolonged hospitalizations, long-term drug treatments, and at least two operations.

Parallel to the increasing number of arthroplasty cases, revision due to aseptic loosening and two-stage revision cases due to periprosthetic infection are also increasing. The cost of managing knee revisions is expected to increase as an issue for patients, physicians, and healthcare institutions [7]. Recent research on this subject is limited because the stated costs are estimated costs. Readmissions, prolonged hospital stays, long-term medication use, and prolonged post-operative rehabilitation times account for many of these high costs. However, more evidence-based information is needed to support these measurements [8]. Existing studies have limitations because they either report estimates rather than actual costs, provide no comparison group (such as cases of non-infected primary total knee arthroplasty), or sum up all orthopedic surgery cases rather than report on specific procedures [9-11]. Furthermore, many of these studies needed to analyze the factors contributing to higher costs beyond repeated operations.

This study compared primary arthroplasty operations, revision operations due to aseptic loosening, and two-stage revision procedures due to periprosthetic infection. Our main aim is to determine the costs of certain services such as pharmaceutical services (inpatient and outpatient treatment), medical and surgical supplies, anesthesia services, diagnostic and radiographic evaluations, operating room services, laboratory costs, blood products, and consultation services in these groups.

METHODS

This study was conducted at a single specialized tertiary care center between January 1, 2017, and December 31, 2022. Patient medical records and infection monitoring database were reviewed for 524 patients who underwent total knee arthroplasty in our institution. The patients were followed for one year from the first surgery date. Institutional review board approval was obtained to analyze patient records and data from the current study (approval number: E-15374210-010.06.99-349814).

A total of 76 patients were included in the study and were divided into three separate groups. In the first group, with the help of a computer-generated program, a study group of 25 primary total knee arthroplasty with no infection matched in terms of type of surgical procedure, date of surgery, age, and gender parameters was formed. In the second group, 27 patients who underwent revision surgery due to radiological aseptic loosening in Ewald and did not develop complications in their follow-up were included. Aseptic loosening criteria, as stated in Ewald, 1) radiolucent lines <2 mm regardless of their localization and progression, 2) the

presence of radiolucent lines reaching the tibial plateau surface, 3) radiolucent lines in the tibial zone 5-6-7, 4) progressive radiolucent lines are has been accepted [12]. The third group consisted of 24 patients who had only deep or joint cavity infections and needed a two-stage revision following their primary procedure. A new definition of PJI has recently been proposed by the European Bone and Joint Infection Society (EBJIS) [13]. Based on this definition, only deep infections characterized by extension into the joint space or deep fascial layers were included in the study. This group did not include patients who underwent debridement and washing due to early postoperative infection and superficial infections. There were no deaths for all three cohorts in our study.

Post-operative care is standard for all patients and includes post-operative dressing with iodine solution at intervals of 48 hours, pain control, empirical antibiotic therapy, use of pharmaceutical agents for anti-embolic prosody, and physical therapy and rehabilitation studies.

The detailed documents of the operation costs, anesthesia, and operating room costs, consultation costs, pharmaceutical agents costs, laboratory costs, blood center expenses, microbiology expenses, radiology expenses, and bed and attendant fees of the patients included in the study were obtained from the purchasing and statistics department of our hospital. Operating room costs include implants, intravenous solutions, surgical supplies, and post-operative recovery. Fees are charged to the laboratory for biochemistry, hematology, urology, immunology, microbiology, and histological specimen processing. Radiology costs include x-rays, ultrasound, computed tomography, and magnetic resonance imaging scans. The consultation fees obtained in this study include those from pulmonology, cardiology, and other internal branches in inpatient and outpatient settings.

Statistical Analysis

Microsoft Excel spreadsheet program (Version 2013, Microsoft Corporation) was used for data collection, comparison, and calculations. Statistical analysis of the study's data was performed using the SPSS for Windows 23.0 program (SPSS Inc). The mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics. The distribution of the variables was measured using the Kolmogorov-Smirnov test. In the comparison of two independent groups showing normal distribution, two Independent t-tests were performed, and One-way Analysis of Variance (One-Way ANOVA) was used to compare more than two groups. The Kruskal–Wallis H test was performed to investigate differences between more than two independent groups that did not conform to normal distribution. When there was a difference between the groups, to determine from which group or groups this difference originated, the Mann–Whitney U test was used to compare the two groups. The chi-squared test was used for categorical variables. Statistical significance was set at a P-value of less than 0.05.

RESULTS

Out of the 76 patients, 60.5% were female and 39.5% were men. The mean age was 65.5±16 years. While 7 (28%) of 25 patients who underwent primary arthroplasty were smoking, 6 (22.2%) of 27 patients who underwent one-stage revision were smokers. Of the 24 patients who underwent two-stage revision, 8 (33.3%) were smokers. There was no statistical difference between the groups (P=0.78).

The age and sex distribution did not differ significantly in the aseptic and septic groups (P>0.05) (Table 1). In the septic group, length of stay, surgery time, service expenses, drug, laboratory, radiology, operation-anesthesia, blood and blood product, consulting, intensive care, and policlinic expenses were significantly higher than the aseptic group (P<0.001) (Table 2).

The median hospital stay was 21 (min 2 and max 42) days in the group that underwent two-stage revision surgery due to periprosthetic knee infection, and this duration was significantly higher than 3.5 days (between 2-8 days) in the group that underwent primary total knee arthroplasty (P<0.001).

The mean number of readmissions in the two-stage knee revision group was 5.6 (range, 2 to 9), the mean was 2.4 in the single-stage knee revision group (range, 2 to 4), and the mean in the primary total knee arthroplasty group was 0.12 (range, 0 to 2) (P<0.001).

When the hospitalization and service fees of the patients in the groups were compared, it was found that the average of 112.39 Turkish Lira (₺) in the primary arthroplasty group, 222.15 ₺ in the patients who

Table 1. Descriptive characteristics of the data

Characteristisc	Data	
Age (years)	65±16	58 (40-81)
Gender		
Female	46 (60%)	
Male	30 (40%)	
Cigarette		
Use	16 (21%)	
Not Use	60 (79%)	
Length of stay (days)	23±19	21 (3-42)
Surgery time (min)	209.34±86.42	150 (90-300)
Service expenses	1889±1258	350 (78-12150)
Drug expenditures	1841±313	1370 (88.9-2876)
Laboratory expenses	258.54±205	124 (32-530)
Radiology expenses	90.2±45.4	98 (39.99-156)
Operation, anesthesia expenses	19045.74±12012	18622 (3650-32678.88)
Blood and blood product expenses	1653.54±1664	461 (14-3745.8)
Consulting expenses	261.75±260	42 (0-580.99)
Intensive care	414.78±367	420 (0-780)
Policlinic	148.88±93.14	111 (30-286)
Total	23452±16154	20008 (4799-43308.73)

Data are shown as mean±standard deviation or median (minimum-maximum). Expenditure amounts are stated in **TL(₺)**.

underwent one-stage revision, and 1027.04 ₺ in the patients who underwent two-stage revision (Fig. 1). In the statistical study, it was found to be significant between the groups (P<0.001). The cost difference is thought to be high due to the extended stay in the service and the large number of medical supplies used in patients who underwent two-stage revision.

When the operation and operating room expenses of the patients were compared, it was found that the average of the patients who underwent primary arthroplasty was 5583.21 ₺, and the patients who underwent one-stage revision were 13301.30 ₺. In comparison, the average of the patients who underwent two-stage revision was 31592.44 ₺ (Fig. 1). A statistically sig-

Table 2. Comparison of primary, aseptic reasons, one-stage revision and septic reasons, two-stage revisions knee arthroplasty data

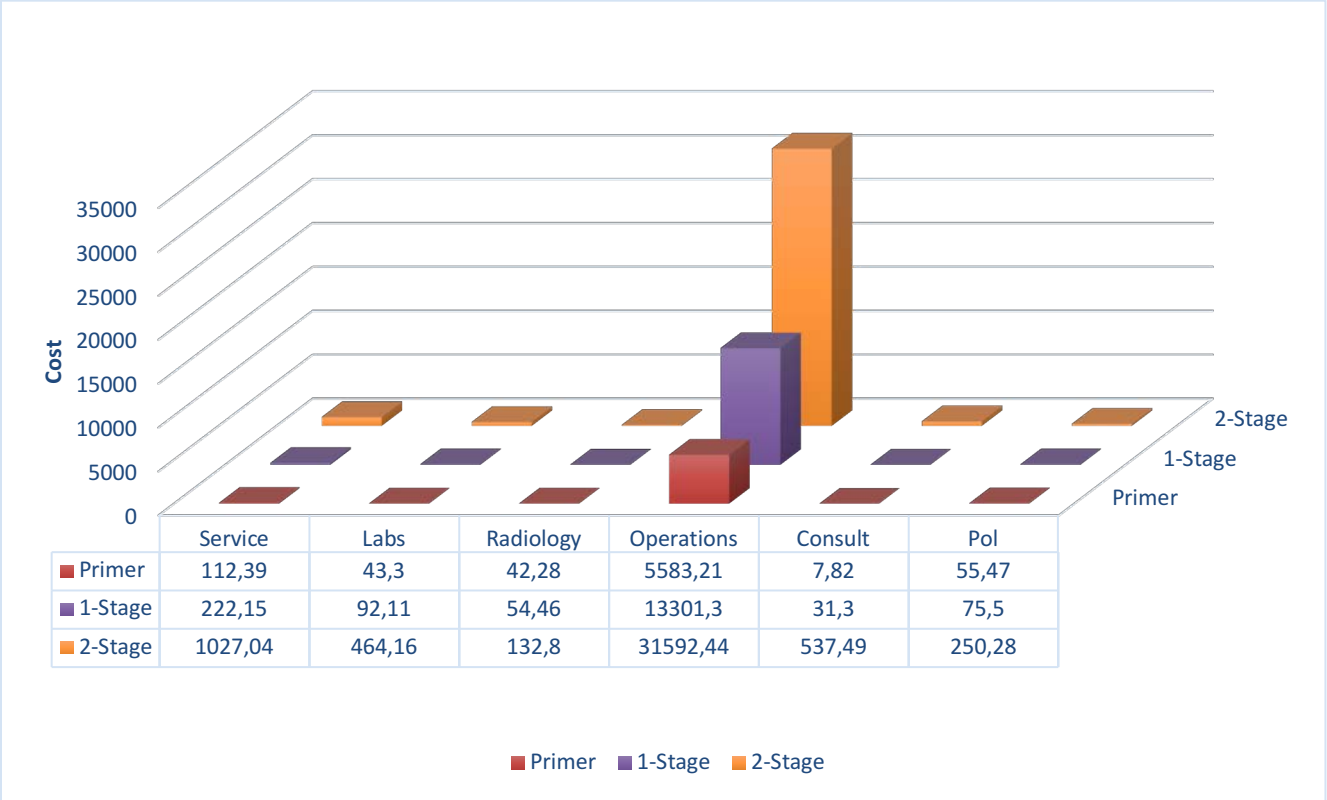
	Primary	Aseptic reasons, one-stage revision	Septic reasons, two-stage revisions	P value
Length of stay (days)	3 (2-4)	6 (3-7)	27 (18-49)	**<0.001**
Surgery time (min)	90 (75-120)	150 (120-180)	270 (180-320)	**<0.001**
Service expenses	98.98 (78-176)	135.56 (78-350)	1051.31 (467-1210)	**<0.001**
Drug expenditures	168 (88.9-189)	189 (88.9-3410)	2987.33 (1987-3865)	**<0.001**
Laboratory expenses	42 (32-56)	46 (32-245)	496 (126-530.79)	**<0.001**
Radiology expenses	38 (32-46)	40.12 (39.99-150)	135 (110-156)	**<0.001**
Operation, anesthesia expenses	3890 (3650-4980)	6120 (3650-19769)	31864 (18111-32678)	**<0.001**
Blood and blood product expenses	14 (14-28)	103 (14-464)	3354.78 (230-3745)	**<0.001**
Consulting expenses	12 (0-48)	19.37 (0-68)	510 (42-580.99)	**<0.001**
Intensive care expenses	0	89.36 (0-420)	780 (0-780)	**<0.001**
Policlinic expenses	49 (30-67)	66.82 (30-131)	216 (49-286)	**<0.001**
Total	5689 (4799-8294)	8294.97 (4799-21174)	40919.67 (19362-43308)	**<0.001**

Data are shown as median (minimum-maximum). Expenditure amounts are stated in **TL(₺)**.

nificant difference exists between the groups (P<0.001). The fact that patients who underwent two-stage revision underwent multiple operations and the cost of the revision implants used confirms this difference.

When the pharmacological costs were compared, the mean of the primary arthroplasty group was 141.66 ₺, and the mean of the patients who underwent one-stage revision was 389.17 ₺. The mean of the patients who underwent two-stage revision was 2964.79 ₺ (Fig. 2). These data were found significant when compared (P<0.001). The high cost of pharmacological agents in two-stage revisions can be attributed to the fact that they received both prophylactic and agent-specific antibiotics during the hospitalization, the lengthening of the hospitalization period, and the increase in the agents used due to additional patients.

When the blood products of the patients were added up, it was found that the average of patients who underwent primary arthroplasty was 34.17 ₺. In comparison, it was 182.96 ₺ for the patients who underwent one-stage revision and 3430.19 ₺ for those who underwent two-stage revision (Fig. 2). A significant statistical difference was found between the groups (P<0.001). The fact that the cost of blood products of patients who underwent two-stage revision is relatively high indicates that the need for blood product transfusion is high in preparation for the operation, during and after the operation.



	Service	Labs	Radiology	Operations	Consult	Pol
Primer	112,39	43,3	42,28	5583,21	7,82	55,47
1-Stage	222,15	92,11	54,46	13301,3	31,3	75,5
2-Stage	1027,04	464,16	132,8	31592,44	537,49	250,28

Fig. 1. **Distribution of significant expenditure items among groups. Expenditure amounts are stated in TL(₺).**

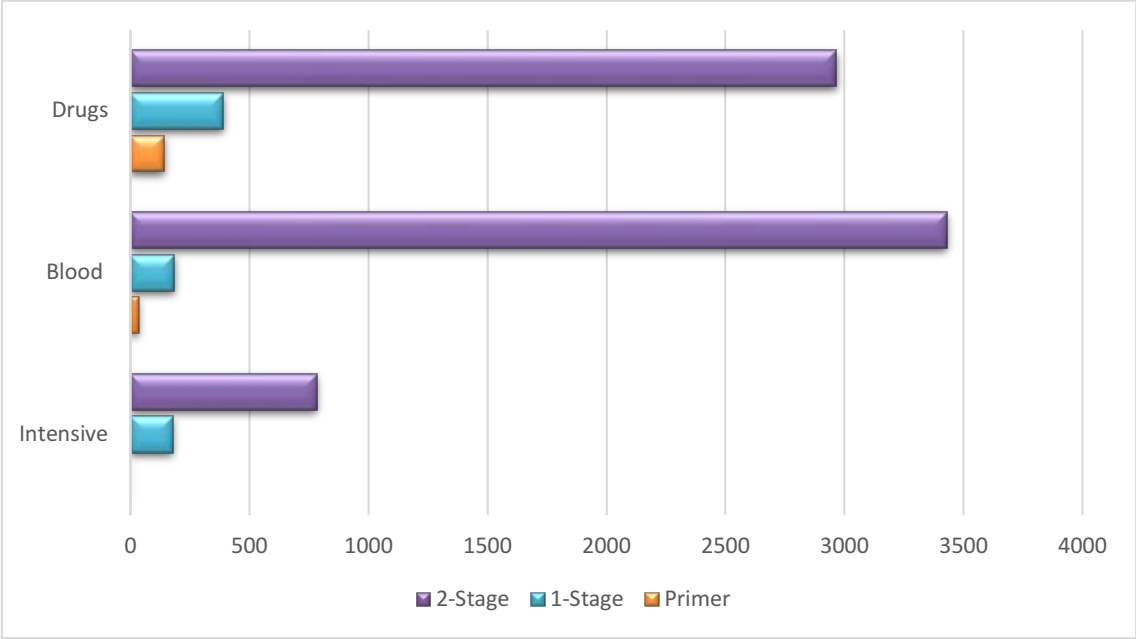


Fig. 2. **Comparison of intensive care-blood products-drug cost between groups.**

When the intensive care unit expenses of the patients were added up, it was seen that the patients who underwent primary arthroplasty did not need intensive care. While the mean of patients who underwent one-stage revision was 177.69 ₺, it was found to be 780.00 ₺ for patients who underwent two-stage revision (Fig. 2). When the data were compared, it was found to be statistically significant, and it was found that the cost of intensive care increased due to the increase in the number of operations and revision operations being more complex and taking longer (P<0.001).

DISCUSSION

As a result of advancing technological opportunities and increasing comfort expectations, the number of hospital applications and operations is rising daily. As a result of the increase in the elderly population, orthopedic prosthesis operations are increasing not only in our country but also worldwide. As a result of the increase in primary arthroplasty operations, revision operations are also increasing in parallel [14-16]. At the same time, the incidence of periprosthetic knee infections is increasing [10]. Managing these infections often requires two-stage revision procedures, which can cost more than mechanical failure and/or aseptic loosening revisions [17].

In our study, we aimed to reveal the cost items of primary arthroplasty and revision operations and to draw attention to the burden on the health system. Two-stage revision costs due to periprosthetic infection were observed to triple the costs of revision procedures due to aseptic loosening. In these infections, the increasing resistance of microorganisms and the ineffectiveness of antibiotic treatments are blamed. For this reason, the doses of antibiotics are increased, and the duration of use is prolonged. Patients require long-term hospitalization, and in some cases, additional operations may be necessary. Therefore, the prevention of periprosthetic infections is essential for reducing health expenditures.

The results of our study were similar to previous studies evaluating the economic impact of surgical site infections following total knee joint arthroplasty [17-20]. Kapadia *et al*., mean episode cost, length of hospital stay, and median readmissions were significantly higher in the infected group compared to the matched cohort: $88,623 to $25,659, 7.6 to 3.29 days, and 2 to 0. Periprosthetic care after TKA was approximately the cost of the episode. It was caused by a 3-fold, 2-fold increase in the average length of hospital stay and an increase in the median readmission time [20]. Periprosthetic infections following TKA represent a tremendous economic burden for tertiary-care centers and patients [19].

It has been observed in the literature that when it comes to septic-based revision surgery, the cost of blood products and drugs is significantly higher during inpatient treatment [21]. A cost analysis of septic total knee revision surgeries should include all costs covered by the hospital, including two separate hospitalizations for the two-stage revision and personnel costs [22]. This study is important because it takes into account all costs incurred during inpatient treatment covered by the hospital, including hospitalization duration, medication, treatment, surgery, anesthesia, laboratory tests, imaging, blood center services, consultation, visits, meal costs, total costs, and billing expenses. The study found that the costs incurred in the septic group were significantly higher than the aseptic group (P<0.001).

Minimizing the number of revisions per patient is crucial in reducing the overall cost burden of revision. This can be achieved by adopting a comprehensive approach that includes optimal patient selection, prosthesis selection, and procedure selection for primary TKA [23, 24]. Careful evaluation of patient characteristics, such as age, weight, and comorbidities, is necessary to select the most appropriate prosthesis and procedure. In addition to these measures, reducing the number of primary TKA surgeries can be achieved through effective non-operative knee osteoarthritis management. This may include weight management programs to combat obesity, exercise programs to improve joint flexibility and strength, and lifestyle changes to reduce the risk of joint injury. By implementing these strategies, the incidence of revision surgeries can be reduced, and the overall cost burden of TKA can be minimized.

The financial burden of septic revision TKA with re-revision can be significantly higher, up to 2.5 times, compared to septic revision alone. Similarly, it can be up to 4 times higher than aseptic revision when re-revision is not required. However, cost savings can be realized by minimizing the occurrence of primary

TKA that develop PJI, avoiding re-revisions for PJI, and shortening the length of hospitalization following revision surgery [25].

Limitations

This study has some limitations. Differences in patients' socioeconomic status may have introduced confounding factors among cohorts, leading to an over- or underestimation of inconsistencies in costs, number of readmissions, and length of hospitalization. However, to minimize any potential bias, patients were selected into groups and matched with the help of a computer-aided program according to the type of surgical procedure, date of surgery, age, and gender parameters. Other limitations are the short follow-up period, the small number of subjects, and the study's retrospective nature. Longer follow-up, larger sample sizes, and prospective multicenter studies are needed to analyze this patient population better. In light of the COVID pandemic, many countries, including Turkey, have been experiencing economic difficulties. It has been observed that the costs of many healthcare practices, materials and revision knee arthroplasty have increased over the years [26, 27]. However, it is important to note that the study conducted had a limitation in terms of fair cost distribution between groups based on the number of years, as it was a direct cost comparison study. Due to these limitations, the real economic and personal impact seen in the cohort undergoing two-stage revision surgery may be more significant than it is.

CONCLUSION

Preventing and treating periprosthetic infections is costly and challenging. We need more research to develop effective protocols and reduce costs. As the number of patients undergoing knee arthroplasty is expected to rise, healthcare systems must ensure the sustainability of public financial resources, especially in public university hospitals.

Ethics approval

This retrospective study was conducted with the approval of the Ondokuz Mayıs University clinical research ethics committee (approval number: E-15374210-010.06.99-349814). Institutional Review Board approval and informed consent of the patients were obtained.

The institution where the study was carried out

Department of Orthopaedics and Traumatology, Ondokuz Mayis University Hospital, Samsun, Türkiye

Authors' Contribution

Study Conception: AY, FS; Study Design: AY; Supervision: FS; Funding: N/A; Materials: AE, CŞŞ; Data Collection and/or Processing: AY, AE, CŞŞ; Statistical Analysis and/or Data Interpretation: AY, AE, CŞŞ; Literature Review: AY, AE; Manuscript Preparation: AY, AE, CŞŞ and Critical Review: AY, AE, FS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Long H, Liu Q, Yin H, et al. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. Arthritis Rheumatol. 2022;74(7):1172-1183. doi: 10.1002/art.42089.
2. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012;27(8 Suppl):61-65.e1. doi: 10.1016/j.arth.2012.02.022.
3. Klug A, Gramlich Y, Rudert M, et al. The projected volume of primary and revision total knee arthroplasty will place an immense burden on future health care systems over the next 30 years. Knee Surg Sports Traumatol Arthrosc. 2021;29(10):3287-3298. doi: 10.1007/s00167-020-06154-7.
4. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev. 2014;27(2):302-345. doi: 10.1128/CMR.00111-13.
5. Gbejuade HO, Lovering AM, Webb JC. The role of microbial biofilms in prosthetic joint infections. Acta Orthop. 2015;86(2):147-158. doi: 10.3109/17453674.2014.966290.
6. Leonard HA, Liddle AD, Burke O, Murray DW, Pandit H. Single- or two-stage revision for infected total hip arthroplasty? A systematic review of the literature. Clin Orthop Relat Res. 2014;472(3):1036-1042. doi: 10.1007/s11999-013-3294-y.
7. Kurtz SM, Ong KL, Schmier J, et al. Future clinical and economic impact of revision total hip and knee arthroplasty. J Bone Joint Surg Am. 2007;89 Suppl 3:144-151. doi: 10.2106/JBJS.G.00587.
8. Senthi S, Munro JT, Pitto RP. Infection in total hip replacement: meta-analysis. Int Orthop. 2011;35(2):253-260. doi: 10.1007/s00264-010-1144-z.

9. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol. 2002;23(4):183-189. doi: 10.1086/502033.
10. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty. 2008;23(7):984-991. doi: 10.1016/j.arth.2007.10.017.
11. Parvizi J, Pawasarat IM, Azzam KA, Joshi A, Hansen EN, Bozic KJ. Periprosthetic joint infection: the economic impact of methicillin-resistant infections. J Arthroplasty. 2010;25(6 Suppl):103-107. doi: 10.1016/j.arth.2010.04.011.
12. Bonnin M, Deschamps G, Neyret P, Chambat P. [Revision in non-infected total knee arthroplasty: an analysis of 69 consecutive cases]. Rev Chir Orthop Reparatrice Appar Mot. 2000;86(7):694-706. [Article in French].
13. Sousa R, Ribau A, Alfaro P, et al. The European Bone and Joint Infection Society definition of periprosthetic joint infection is meaningful in clinical practice: a multicentric validation study with comparison with previous definitions. Acta Orthop. 2023;94:8-18. doi: 10.2340/17453674.2023.5670.
14. Barret M WE, Whalen D. Summary 2007 HCUP Nationwide Inpatient Sample (NIS) Comparison Report. HCUP Method Series Report # 2010-03. Online September 9, 2010. U.S. Agency for Healthcare Research and Quality.
15. Ollenschläger G. Assuring the Quality of Health Care in the EU: Germany. In book: Assuring the Quality of Health Care in the European Union. A case for action. Ed.: European Observatory Studies Series Nr 12, WHO Publication: Copenhagen, 2008: pp. 116-120.
16. Mark Allen Group. Hospital non-compliance risking joint patient safety. Br J Hosp Med. 2012;73(10):548. doi: 10.12968/hmed.2012.73.10.548a.
17. Bozic KJ, Ries MD. The impact of infection after total hip arthroplasty on hospital and surgeon resource utilization. J Bone Joint Surg Am. 2005;87(8):1746-1751. doi: 10.2106/JBJS.D.02937.
18. Hebert CK, Williams RE, Levy RS, Barrack RL. Cost of treating an infected total knee replacement. Clin Orthop Relat Res. 1996;(331):140-145. doi: 10.1097/00003086-199610000-00019.
19. Kapadia BH, McElroy MJ, Issa K, Johnson AJ, Bozic KJ, Mont MA. The economic impact of periprosthetic infections following total knee arthroplasty at a specialized tertiary-care center. J Arthroplasty. 2014;29(5):929-932. doi: 10.1016/j.arth.2013.09.017.
20. Kapadia BH, Banerjee S, Cherian JJ, Bozic KJ, Mont MA. The Economic Impact of Periprosthetic Infections After Total Hip Arthroplasty at a Specialized Tertiary-Care Center. J Arthroplasty. 2016;31(7):1422-1426. doi: 10.1016/j.arth.2016.01.021.
21. Dırvar F, Dırvar SU, Yıldırım T, Cengiz Ö, Talmaç MA. Cost Analysis in Knee Revision Arthroplasty: A Study at the Research and Training Hospital in Turkey. JAREM J Acad Res Med. 2020;10(2):133-137. doi: 10.4274/jarem.galenos.2020.2767.
22. Kasch R, Merk S, Assmann G, et al. Comparative Analysis of Direct Hospital Care Costs between Aseptic and Two-Stage Septic Knee Revision. PLoS One. 2017;12(1):e0169558. doi: 10.1371/journal.pone.0169558.
23. Vertullo CJ, Graves SE, Peng Y, Lewis PL. An optimum prosthesis combination of low-risk total knee arthroplasty options in all five primary categories of design results in a 60% reduction in revision risk: a registry analysis of 482,373 prostheses. Knee Surg Sports Traumatol Arthrosc. 2019;27(5):1418-1426. doi: 10.1007/s00167-018-5115-z.
24. Adie S, Harris I, Chuan A, Lewis P, Naylor JM. Selecting and optimising patients for total knee arthroplasty. Med J Aust. 2019;210(3):135-141. doi: 10.5694/mja2.12109.
25. Okafor C, Hodgkinson B, Nghiem S, Vertullo C, Byrnes J. Cost of septic and aseptic revision total knee arthroplasty: a systematic review. BMC Musculoskelet Disord. 2021;22(1):706. doi: 10.1186/s12891-021-04597-8.
26. Ashkenazi I, Christensen T, Ward SA, et al. Trends in Revenue and Cost for Revision Total Knee Arthroplasty. J Arthroplasty. 2023;38(7 Suppl 2):S97-S102. doi: 10.1016/j.arth.2023.01.041.
27. Lopez-Villegas A, Bautista-Mesa RJ, Acosta-Robles P, et al. Analysis of Healthcare Costs Incurred in Regional Hospitals in Andalusia (Spain) during the COVID-19 Pandemic. Int J Environ Res Public Health. 2022;19(23):16132. doi: 10.3390/ijerph192316132.

The European Research Journal 2024;10(6):609-616 Original Article

DOI: https://doi.org/10.18621/eurj.1457903 *Orthopaedic and Traumatology*

Comparison of plate and compression screw in the treatment of hallux rigidus with arthrodesis: a retrospective study

Ahmet Yurteri[1], Numan Mercan[2], Ahmet Yıldırım[3]

[1]Department of Orthopaedics and Traumatology, Konya City Hospital, Konya, Türkiye, [2]Department of Orthopaedics and Traumatology, Necip Fazıl City Hospital, Kahramanmaraş, Türkiye, [3]Department of Orthopedics and Traumatology, University of Health Sciences, Health Application and Research Center, Konya, Türkiye

ABSTRACT

Objectives: Although numerous surgical techniques and fixation methods have been described for the treatment of hallux rigidus (HR) with arthrodesis, consensus on the gold standard treatment has not been reached. The aim of this study is to retrospectively compare the clinical and radiological outcomes of compression screw fixation and plate fixation in the treatment of HR with arthrodesis.

Methods: Patients who underwent arthrodesis surgery due to HR between January 2021 and December 2023 at a single center were retrospectively reviewed. Patients who met the inclusion criteria were divided into two groups: those who underwent arthrodesis with plate fixation (PLATE) and those who underwent arthrodesis with compression screw fixation (SCREW). Demographic data including age, gender, affected side, operative time, hallux valgus angle (HVA), dorsiflexion angle, AOFAS scores, and implant irritation data were compared among patients with at least 3 months of follow-up.

Results: It was observed that all patients included in the study had successful bone union without any complications. There were no significant differences between the two groups in terms of age, gender, affected side, preoperative HVA, and preoperative AOFAS scores (P= 0.970, P= 0.426, P= 0.694, P= 0.216, and P= 0.905, respectively). The mean operation time and postoperative AOFAS score were lower in the PLATE group compared to the SCREW group (P=0.006 and P=0.004, respectively). However, in the SCREW group, the dorsiflexion angle and the rate of implant irritation were lower compared to the PLATE group (P=0.016 and P=0.01, respectively).

Conclusions: In the surgical treatment of HR, both plate fixation arthrodesis and compression screw arthrodesis are reliable surgical techniques. While plate fixation arthrodesis is a faster and more practical method, arthrodesis with a compression screw results in fewer complaints related to the implant and provides a more functional recovery.

Keywords: Hallux rigidus, arthrodesis, treatment, plate, compression screw

Corresponding author: Ahmet Yurteri, MD.,
Phone: +90 332 310 50 00, E-mail: op.drahmetyurteri@gmail.com

How to cite this article: Yurteri A, Mercan N, Yıldırım A. Comparison of plate and compression screw in the treatment of hallux rigidus with arthrodesis: a retrospective study. Eur Res J. 2024;10(6):609-616. doi: 10.18621/eurj.1457903

Received: March 25, 2024
Accepted: May 5, 2024
Published Online: May 30 2024

Hallux rigidus (HR) presents as a clinical condition characterized by limited mobility and pain due to arthrosis of the first metatarsophalangeal joint (MPJ1) [1-3]. The MPJ1 actively participates in the propulsion phase of the gait cycle. However, in various pathological conditions, often painful conditions, this joint can be completely disrupted, leading to a decrease in range of motion (ROM) and restriction of function. At this point, first metatarsophalangeal arthrodesis (MPA1) emerges as a long-standing surgical technique [4-6]. This surgical procedure is preferred to alleviate pain and restore functional activity. It is particularly effective in the treatment of various pathologies, such as HR and severe hallux valgus (HV). However, the success and outcomes of this surgery may vary depending on the techniques employed [7-9].

The MPA1 procedure can vary depending on the type of joint surface resection and fixation method. For instance, these surgeries may rely on different types of joint surface resections, such as flat, concave, or convex, and various fixation methods, including screws, plates, or staples [10-12]. These different techniques can affect the effectiveness and outcomes of the surgical procedure. In most cases, equipment containing a compression system, such as dorsal plates or compression screws, is used for performing MPA1 procedures. However, there is still a lack of widespread consensus among surgeons specializing in foot surgery regarding which method should be considered the gold standard. This situation demonstrates ongoing debates and various perspectives concerning the practical applications of the gold standard [11, 13, 14].

We aim to evaluate the clinical and radiological outcomes by comparing patients undergoing arthrodesis with dorsal plate versus compression screw fixation for MPA1.

METHODS

Ethics Committee Approval and Study Design

The study was initiated after obtaining approval from the Necmettin Erbakan University Ethics Committee with decision number 2023/4836 and conducted in accordance with the principles outlined in the Helsinki Declaration. A retrospective study design was developed to compare the clinical and radiological outcomes of patients undergoing arthrodesis with either a plate or compression screw for MPJ1. Patients diagnosed with symptomatic MPJ1 osteoarthritis between January 2021 and December 2023, who subsequently underwent arthrodesis surgery, were examined. Among these patients, demographic data including age, gender, follow-up duration, affected extremity side, and operation duration were recorded. Patients meeting the inclusion criteria were divided into two groups: those who underwent arthrodesis with plate

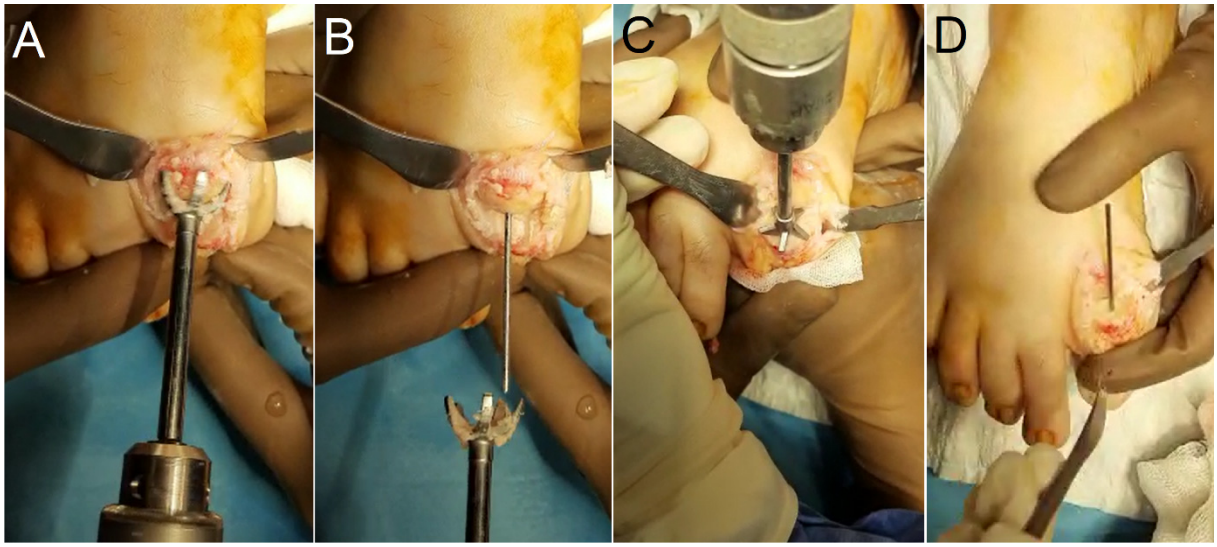


Fig. 1. Preparation of ball-cup (convex-concave) arthrodesis surfaces in the screw group.

fixation (PLATE) and those who underwent arthrodesis with screw fixation (SCREW).

Inclusion and Exclusion Criteria

Patients with severe HV defined by an M1/P1 angle greater than 40°, inflammatory diseases (rheumatoid arthritis), or recurrence of HV deformity (secondary surgery), as well as patients with intellectual or mental disorders and those lost to follow-up, were determined as exclusion criteria.

Surgical Procedure

All surgical procedures were performed by a surgeon following antibiotic prophylaxis (1 gram IV cefazolin) and ensuring necessary sterile conditions. After applying a tourniquet to the patient's thigh, an incision was made approximately 0.5- 1 cm above the junction of the dorsal and plantar surfaces at the level of the MPJ1, from the superomedial aspect of the toe. Capsulotomy of the MPJ1 was performed, and osteophytes around the joint were excised. Up to this point, the surgical procedure was similar for both techniques.

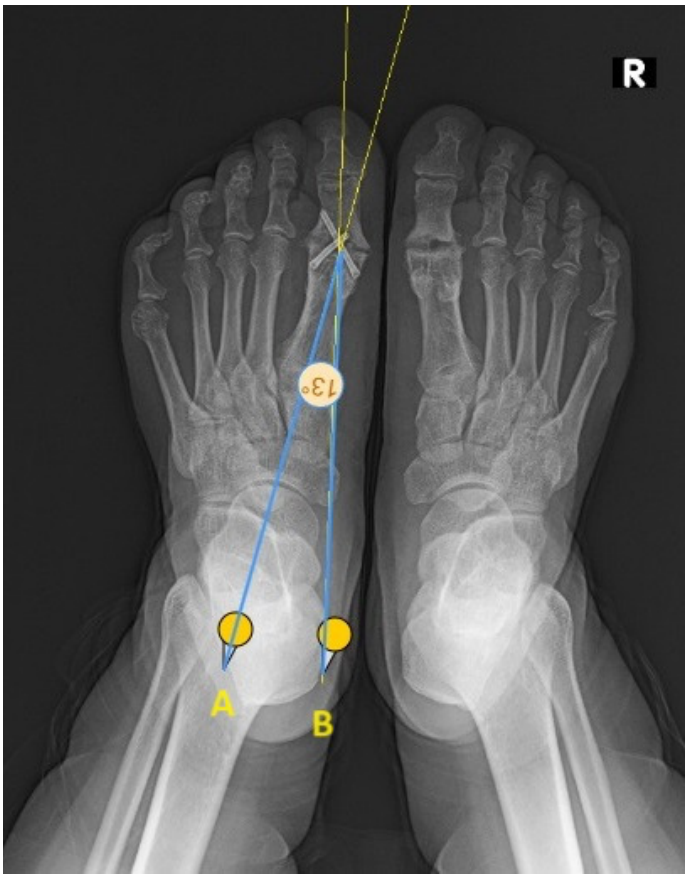


Fig. 2. Hallux valgus angle measurement. (A) 1. Metatarsal diaphyseal axis; (B) Proximal phalanx diaphyseal axis.

For the PLATE group, the distal articular surface of the first metatarsal and the proximal phalanx were excised with osteotomy, and stabilization for osteosynthesis was achieved by placing a plate and locking screws on the dorsal surface under fluoroscopic guidance. In the SCREW group, the articular surfaces were prepared using a motorized concave-convex drilling technique, guided by a previously aligned K-wire, which was aligned with the diaphyseal axis of the first metatarsal and the first phalanx of the hallux. Reamirization of the articular surface continued until pinpoint bleeding was observed in the subchondral bone (Fig. 1A-D). Subsequently, fixation for osteosynthesis was achieved under fluoroscopy with two compression screws. In both surgical procedures, arthrodesis was applied with neutral rotation, 5°-15° valgus, and a dorsiflexion angle of a 5°- 15° according to the ground (20°- 25° relative to the first metatarsal).

After confirming the position of arthrodesis and fixation material under radioscopic control, the skin was closed with 4.0 monofilament sutures, and a compressive bandage was applied to the foot and ankle. The same rehabilitation program was applied for both surgical procedures; patients were advised to use a splint for three weeks postoperatively and were instructed not to bear weight on the operated extremity during this period. After this time, they were allowed to bear weight with the assistance of rigid-soled shoes for four weeks, followed by gradually transitioning to normal shoes with weight-bearing allowed thereafter.

Radiological and Clinical Evaluation

X-ray images were taken with weight-bearing on the affected toe to measure the preoperative and postoperative hallux valgus angle (HVA) and postoperative dorsiflexion angle (DFA). The HVA measurement is determined as the angle formed between the line indicating the longitudinal axis of the first metatarsal bone and the line indicating the longitudinal axis of the proximal phalanx on the dorsoplantar radiograph (Fig. 2). The DFA is determined as the angle formed between the line indicating the longitudinal axis of the first metatarsal bone and the line indicating the longitudinal axis of the proximal phalanx on the lateral radiograph (Fig. 3). To evaluate patients' functional capacities, preoperative and postoperative AOFAS

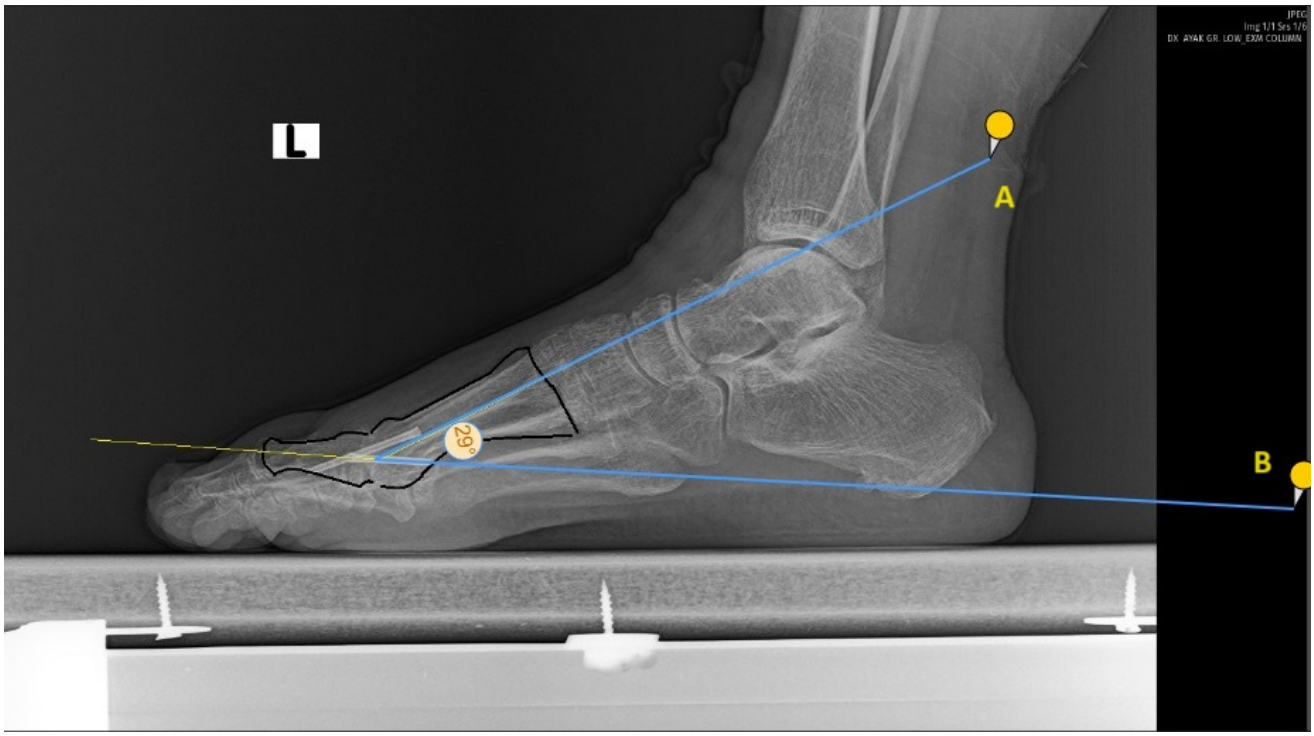


Fig. 3. Dorsiflexion angle measurement. (A) 1. Metatarsal lateral diaphyseal axis; (B) Proximal phalanx lateral diaphyseal axis.

scores (American Orthopaedic Foot & Ankle Society) were examined. Additionally, patients were questioned about whether the implant used in the postoperative period caused any irritation during their latest follow-up appointments.

Statistical Analysis

The data were analyzed using Stata version 16 statistical software (StataCorp LLC, College Station, TX, USA). All samples were examined together, and the two groups were compared with each other based on the treatment type received. For quantitative variables, the Student's t-test was used, and for qualitative variables, the Chi-square test was employed. A significance level of $P<0.05$ was considered statistically significant.

RESULTS

Out of 47 operated patients, 32 toes (from 31 patients) meeting the inclusion criteria were included in the evaluation. Among them, 14 toes underwent arthrodesis with a plate, while 18 toes underwent arthrodesis with a compression screw. It was observed that all evaluated patients had successful bone union, and there were no major complications such as nonunion, implant failure, or reoperation. Only one patient in the SCREW group experienced intraoperative guide wire breakage, resulting in an intramedullary guide remaining in the first metatarsal, which could not be removed. However, this situation did not cause pain complications in the patient, and successful bone union was observed, so it was considered a minor complication.

The average follow-up duration was 8.42±4.55 (range: 3-19) months in the PLATE group and 7.83±5.84 (range: 3-28) months in the SCREW group, with no significant difference observed between the two groups (P=0.434). In the PLATE group, the mean age was 55.71±12.16 years (range: 38- 74), while in the SCREW group, it was 55.50±8.35 years (range: 42-72), with no significant difference observed between the two groups (P=0.970). The male/female ratio in the PLATE group was 2/12 (14.3%/85.7%), while in the SCREW group, it was 5/13 (27.8%/72.2%), with no significant difference observed between the two groups (P=0.426). The af-

fected extremity side (left or right) in the PLATE group was 3/11 (21.4%/78.6%), while in the SCREW group, it was 6/12 (33.3%/66.7%), with no significant difference observed between the two groups (P= 0.694). The mean operation duration was 37.14±11.03 minutes (range: 25-64) in the PLATE group and 50.44±13.72 minutes (range: 28-71) in the SCREW group, with a significant difference observed between the two groups (P=0.006) (Table 1).

In radiological measurements, the preoperative HVA was 16.29±6.7 (range: 9-29) in the PLATE group and 13.72±8.98 (range: 3-32) in the SCREW group, with no significant difference observed between the two groups (P=0.216). The postoperative HVA was 4.71±2.36 (range: 1-9) in the PLATE group and 3.61±2.38 (range: 0-8) in the SCREW group, with no significant difference observed between the two groups (P=0.206). The change in HVA (preoperative-postoperative) was 11.57±6.81 (range: 3-23) in the PLATE group and 10.11±8.91 (range: 0-31) in the SCREW group, with no significant difference observed between the two groups (P=0.350). The postoperative DFA was 28.79±6.81 (range: 14-36) in the PLATE group and 22.89±6.23 (range: 12-33) in the SCREW group, with a significant difference observed between the two groups (P= 0.016) (Table 1).

In the PLATE group, the preoperative AOFAS score was 28.57±4.58, while in the SCREW group, it was 27.66±6.49, with no significant difference observed between the two groups (P=0.905). The postoperative AOFAS score was 72.14±13.40 in the PLATE group and 85.83±6.47 in the SCREW group, with a significant difference observed between the two groups (P= 0.004). Complaints related to implant irritation were observed in 5 patients (35.7%) in the PLATE group, while none were observed in the SCREW group, indicating a significantly higher rate of implant irritation in the PLATE group (P=0.01) (Table 1).

Table 1. Comparison of parameters of PLATE and SCREW group

Parameter	PLATE group	SCREW group	P value
Age (years)	55.71±12.16 (38-74)	55.50±8.35 (42-72)	0.970[a]
Gender (Male/female)	2/12 (14.3%/85.7%)	5/13(27.8%/72.2%)	0.426[b]
Side (Left/right)	3/11 (21.4%/78.6%)	6/12 (33.3%/66.7%)	0.694[b]
Operation time (minutes)	37.14±11.03 (25-64)	50.44±13.72 (28-71)	**0.006[a]**
Follow-up duration (months)	8.42±4.55 (3-19)	7.83±5.84 (3-28)	0.434[b]
Preoperative HVA	16.29±6.7 (9-29)	13.72±8.98 (3-32)	0.216[a]
Postoperative HVA	4.71±2.36 (1-9)	3.61±2.38 (0-8)	0.206[a]
HVA change	11.57±6.81 (3-23)	10.11±8.91 (0-31)	0.350[a]
DFA	28.79±6.81 (14-36)	22.89±6.23 (12-33)	**0.016[a]**
Preoperative AOFAS score	28.57±4.58	27.66±6.49	0.905[a]
Postoperative AOFAS score	72.14±13.40	85.83±6.47	**0.004[a]**
Implant irritation	5 (35.7%)	0 (0%)	**0.010[b]**

Data are shown as mean±standard deviation (minimum-maximum) or n (%). HVA=Hallux valgus angle, DFA=Dorsiflexion angle, AOFAS=American Orthopaedic Foot & Ankle Society

[a]Mann-Withney U test, [b]Fisher's exact test

DISCUSSION

Both plating and compression screw procedures are reliable surgical treatments for treating HR with arthrodesis. Although plating is a quicker and more convenient method, it has been shown that compression screw arthrodesis leads to fewer issues connected to the implant and offers superior functional recovery. Similarities were observed between the two groups in terms of age, gender, follow-up duration, preoperative and postoperative HVA, HVA change, and preoperative AOFAS scores. The only advantage that could be considered for those undergoing arthrodesis with a plate was the shorter operation duration. The main advantages observed for those undergoing arthrodesis with a compression screw compared to those with a plate were higher postoperative AOFAS scores, fewer complaints related to implant irritation, and DFA being closer to the optimal angle range. These results not only support the safe use of both surgical techniques in the treatment of HR with arthrodesis but also suggest that patient satisfaction is higher in arthrodesis with a compression screw prepared with ball-cup reaming.

In our study, the mean age of the included patients was 55 years, and the predominance of female gender was consistent with previous studies [14-16]. Furthermore, prior studies have demonstrated high fusion rates for MPA1, with Coughlin *et al*. [17] reporting 98%, Flavin *et al*. [18] reporting 100% fusion rates, and Goucher *et al*. [19] reporting 92%. Our study's finding of 100% fusion in the included patients aligns with these previous findings in the literature. However, Besse *et al*. reported a fusion rate of 74% in a series of 54 MPA1 cases using pure titanium staple fixation with ball and cup reamers [20]. This result suggests that both compression screws and plates provide more stable fixation in MPA1 compared to staples.

Various arthrodesis techniques have been reported in the literature, including cross-screw fixation, staple fixation, single interfragmentary screw fixation, dorsal compression plating, and combined plate and screw fixation [11, 13, 14, 21]. Additionally, differences exist in the preparation of joint surfaces for arthrodesis, such as plane cuttings or conical reaming. Curtis and Politi reported in their cadaver study that conical preparation with interfragmentary screw fixation provides more rigid stabilization compared to both dorsal plating with plane resection and interfragmentary screw fixation [22, 23]. However, Neri *et al*. [16] indicated in their study that joint surfaces prepared with plane resection offer the possibility of arthrodesis in the optimal position without shortening of the first ray. In our study, successful fusion was observed in both types of arthrodesis, indicating that both treatment methods can be safely applied. However, the gold-standard technique remains controversial. Our study suggests that the SCREW technique (conical preparation + interfragmentary screw fixation) is advantageous, as it is associated with fewer complaints related to implant irritation and better AOFAS scores. A disadvantage of this technique is that placing two compressive screws in the appropriate position for the MPJ1 is more challenging and time-consuming compared to plating for arthrodesis.

Postoperatively, there was an average increase of approximately 44 points in the AOFAS score for the PLATE group and 58 points for the SCREW group compared to preoperative scores. Goucher *et al*. [19] reported a 31-point increase in AOFAS score after MPA1 based on conical preparation and dorsal plating fixation. While the increase in AOFAS score in our PLATE group was close to 44 points postoperatively, the notable increase of 58 points in the AOFAS score in the SCREW group in our study is worth mentioning. We believe there are two reasons for this discrepancy. Firstly, Goucher *et al*.'s [19] study included a variety of indications for arthrodesis (such as HV and HR), whereas our study focused solely on patients diagnosed with isolated HR. This is significant because the symptom of pain in HR patients is more prevalent than the deformity seen in HV. Another factor is that Goucher *et al*. [19] performed arthrodesis solely with plating, which inevitably increases the likelihood of implant irritation and decreases satisfaction rates.

In our radiological evaluation, the change in HVA was 11.5° in patients undergoing arthrodesis with plates and 10.1° in those with compression screws, showing a lower angle change compared to the literature. The angle change was larger in studies by Pydah *et al*. [24] (22.6°), Besse *et al*. [20] (25°), and Neri *et al*. [16] (23.2°- 20.4°). We attribute the larger angle change in these studies to the inclusion of patients with severe HV undergoing arthrodesis, whereas in our

study, only patients with MPJ1 osteoarthritis were included. Postoperative DFA was 28.7° in patients with plate arthrodesis and 22.89° in those with compression screw arthrodesis. In a study by Jarabo *et al*. on MPA1, DFA was 21.15° in patients using compression screws along with plates, while it was 28.44° with only plate usage. These values are similar to those obtained in our study. Another important point here is that DFA was higher only in patients undergoing arthrodesis with plates in both our study and the study by Garcia-Jarabo *et al*. [25]. We believe this is due to the compression forces generated between the dorsal surface of the bone and the plate during arthrodesis with plates, resulting in tensile forces on the plantar surface and thus an increased DFA. In contrast, on surfaces prepared with ball cup reaming, compression screws act as interfragmentary screws along the osteotomy line, resulting in less significant increases in DFA.

Limitations

Our study has some limitations. Being retrospective, lack of recording of intraoperative fluoroscopy time, surgeries performed by multiple different surgeons, and the use of implants from different brands are factors that limit the study.

CONCLUSION

In the treatment of HR with arthrodesis, both plating and compression screw techniques are reliable surgical methods. While plating is a faster and more practical approach, it has been observed that compression screw arthrodesis results in fewer implant-related complaints and provides better functional recovery.

Authors' Contribution

Study Conception: AY; Study Design: AY; Supervision: NM; Funding: N/A; Materials: NM; Data Collection and/or Processing: AY; Statistical Analysis and/or Data Interpretation: AYıldırım; Literature Review: NM; Manuscript Preparation: AY and Critical Review: AYıldırım.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grants during the conduct or writing of this study.

Acknowledgments

We would like to thank the surgeons working at Konya City Hospital Orthopedics and Traumatology Clinic Department for sharing the data of the hallux rigidus patients they operated on.

REFERENCES

1. Hamid KS, Parekh SG. Clinical Presentation and Management of Hallux Rigidus. Foot Ankle Clin. 2015;20(3):391-399. doi: 10.1016/j.fcl.2015.04.002.
2. Ho B, Baumhauer J. Hallux rigidus. EFORT Open Rev. 2017;2(1):13-20. doi: 10.1302/2058-5241.2.160031.
3. Yee G, Lau J. Current concepts review: hallux rigidus. Foot Ankle Int. 2008;29(6):637-646. doi: 10.3113/FAI.2008.0637.
4. Gibson JN, Thomson CE. Arthrodesis or total replacement arthroplasty for hallux rigidus: a randomized controlled trial. Foot Ankle Int. 2005;26(9):680-690. doi: 10.1177/107110070502600904.
5. Stevens J, de Bot RTAL, Hermus JPS, van Rhijn LW, Witlox AM. Clinical Outcome Following Total Joint Replacement and Arthrodesis for Hallux Rigidus: A Systematic Review. JBJS Rev. 2017;5(11):e2. doi: 10.2106/JBJS.RVW.17.00032.
6. Stone OD, Ray R, Thomson CE, Gibson JN. Long-Term Follow-up of Arthrodesis vs Total Joint Arthroplasty for Hallux Rigidus. Foot Ankle Int. 2017;38(4):375-380. doi: 10.1177/1071100716682994.
7. Fuhrmann RA. First metatarsophalangeal arthrodesis for hallux rigidus. Foot Ankle Clin. 2011;16(1):1-12. doi: 10.1016/j.fcl.2010.12.003.
8. Lombardi CM, Silhanek AD, Connolly FG, Dennis LN, Keslonsky AJ. First metatarsophalangeal arthrodesis for treatment of hallux rigidus: a retrospective study. J Foot Ankle Surg. 2001;40(3):137-143. doi: 10.1016/s1067-2516(01)80079-x.
9. Aas M, Johnsen TM, Finsen V. Arthrodesis of the first metatarsophalangeal joint for hallux rigidus--optimal position of fusion. Foot (Edinb). 2008;18(3):131-135. doi: 10.1016/j.foot.2008.03.002.
10. Faraj AA, Naraen A, Twigg P. A comparative study of wire fixation and screw fixation in arthrodesis for the correction of hallux rigidus using an in vitro biomechanical model. Foot Ankle Int. 200;28(1):89-91. doi: 10.3113/FAI.2007.0016.
11. Kang YS, Bridgen A. First metatarsophalangeal joint arthrodesis/fusion: a systematic review of modern fixation techniques. J Foot Ankle Res. 2022;15(1):30. doi: 10.1186/s13047-022-00540-9.
12. Schafer KA, Baldini T, Hamati M, Backus JD, Hunt KJ, McCormick JJ. Two Orthogonal Nitinol Staples and Combined Nitinol Staple-Screw Constructs for a First Metatarsophalangeal Joint Arthrodesis: A Biomechanical Cadaver Study. Foot Ankle Int. 2022;43(11):1493-1500. doi: 10.1177/10711007221119157.
13. Shah K, Augustine A, Carter R, McFadyen A. Arthrodesis of

the first metatarsophalangeal joint: comparison of three techniques. J Am Podiatr Med Assoc. 2012;102(1):13-17. doi: 10.7547/1020013.
14. Chien C, Alfred T, Freihaut R, Pit S. First Metatarsophalangeal Joint Arthrodesis in Hallux Valgus Versus Hallux Rigidus Using Cup and Cone Preparation Compression Screw and Dorsal Plate Fixation. Cureus. 2017;9(10):e1786. doi: 10.7759/cureus.1786.
15. Coughlin MJ, Shurnas PS. Hallux rigidus: demographics, etiology, and radiographic assessment. Foot Ankle Int. 2003;24(10):731-743. doi: 10.1177/107110070302401002.
16. Neri T, Beach AB, Farizon F, Philippot RJ. Advantages of a compression screw for the arthrodesis of the first metatarsophalangeal joint of the foot: comparative study.Acta Orthop Belg. 2020;86(Suppl 2):144-151.
17. Coughlin MJ, Abdo RV. Arthrodesis of the first metatarsophalangeal joint with Vitallium plate fixation. Foot Ankle Int. 1994;15(1):18-28. doi: 10.1177/107110079401500105.
18. Flavin R, Stephens MM. Arthrodesis of the first metatarsophalangeal joint using a dorsal titanium contoured plate. Foot Ankle Int. 2004;25(11):783-787. doi: 10.1177/107110070402501105.
19. Goucher NR, Coughlin MJ. Hallux metatarsophalangeal joint arthrodesis using dome-shaped reamers and dorsal plate fixation: a prospective study. Foot Ankle Int. 2006;27(11):869-876. doi: 10.1177/107110070602701101.
20. Besse JL, Chouteau J, Laptoiu D. Arthrodesis of the first metatarsophalangeal joint with ball and cup reamers and osteosynthesis with pure titanium staples Radiological evaluation of a continuous series of 54 cases. Foot Ankle Surg. 2010;16(1):32-37. doi: 10.1016/j.fas.2009.03.008.
21. Roukis TS, Meusnier T, Augoyard M. Nonunion rate of first metatarsal-phalangeal joint arthrodesis with crossed titanium flexible intramedullary nails and a dorsal static staple with immediate weightbearing. J Foot Ankle Surg. 2012;51(2):191-194. doi: 10.1053/j.jfas.2011.10.041.
22. Curtis MJ, Myerson M, Jinnah RH, Cox QG, Alexander I. Arthrodesis of the first metatarsophalangeal joint: a biomechanical study of internal fixation techniques. Foot Ankle. 1993;14(7):395-359. doi: 10.1177/107110079301400705.
23. Politi J, John H, Njus G, Bennett GL, Kay DB. First metatarsal-phalangeal joint arthrodesis: a biomechanical assessment of stability. Foot Ankle Int. 2003;24(4):332-337. doi: 10.1177/107110070302400405.
24. Pydah SK, Toh EM, Sirikonda SP, Walker CR. Intermetatarsal angular change following fusion of the first metatarsophalangeal joint. Foot Ankle Int. 2009;30(5):415-418. doi: 10.3113/FAI-2009-0415.
25. García-Jarabo E, Alonso-Tejero D, Ramos-Ramos LM, Hernanz-González Y, Vilá Y Rico J. Better results in consolidation of hallux metatarsophalangeal arthrodesis with dorsal plate and interfragmentary compression screw. Rev Esp Cir Ortop Traumatol. 2024:S1888-4415(24)00057-2. doi: 10.1016/j.recot.2024.01.030.

The European Research Journal 2024;10(6):617-625 Original Article

DOI: https://doi.org/10.18621/eurj.1506954 *Histology and Embryology*

RETRACTED - Cell transcription dependent on Wingless-type (Wnt)/beta-catenin in the rat estrous cycle stages

Tuğba Dağdeviren

Department of Histology and Embryology, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye

ABSTRACT

Objectives: We aimed to evaluate how T Cell Factor 7 Like 2 (TCF7L2) and Lymphoid Enhancer Factor-1 (LEF-1), which regulate cell transcription, regulate implantation in the endometrium.

Methods: Female rats were determined according to the estrous cycle. The obtained uterine tissues were taken for immunofluorescence staining.

Results: In estrous, LEF-1 and TCF7L2 showed localization in perimetrial-myometrial connective tissue. Of all the signaling molecules, the TCF7L2 molecule is the only one that is expressed. Non-expressed TCF7L2 in the uterine epithelium showed strong immunolocalization in the perimetrial myometrial connective tissue and endometrial basal stroma area. LEF-1 was mostly expressed in the metaestrus phase in the areas of gland epithelium.

Conclusions: TCF7L2 and LEF-1 play a critical role in cell proliferation, differentiation and transcription by regulating the activation of the Wnt signaling pathway in endometrial cells. These findings help us to understand the role of TCF7L2 and LEF-1 in the provision of endometrial homeostasis and in the implantation process.

Keywords: Cell transcription, implantation, rat, T cell factor, lymphoid enhancer factor

During implantation, many signaling molecules are known to play an important role in communication between the blastocyst and the receptive endometrium. In mammals, implantation is a complex and not yet fully understood process involving cellular, hormonal and molecular factors originating from the embryo and endometrium [1, 2]. Successful implantation is possible with precisely arranged reciprocal signaling between the implanted blastocyst and the recipient uterus. Meanwhile, it is defined as a series of processes that involve the embryo first settling in the decidua and then reaching the mother's circulatory system and feeding the placenta. A complex set of dialogue takes place between the endometrium and the embryo through growth factors, hormones, adhesion molecules, cell transcription molecules, and prostaglandins. Thanks to these factors, the embryo adheres to the epithelium, moves towards the basement membrane and invades the stroma. Cellular transcription occurs through various signaling pathways [3]. From these pathways, the Wingless-type (Wnt) signaling pathway plays an important role in the self-renewal of adult cells, cell adhesion, and control of the transcription of target cell genes. In the embryonic period, cell polarity plays a critical role in proliferation, differentiation and cell migration [4]. There are extensive studies in the literature on the Wnt signaling pathway and diseases caused by changes in the

Corresponding Author: Tuğba Dağdeviren, PhD.,
E-mail: dagdevirentuba@gmail.com

How to cite this article: Dağdeviren T. Cell transcription dependent on Wingless-type (Wnt)/beta-catenin in the rat estrous cycle stages. Eur Res J. 2024;10(6):617-625. doi: 10.18621/eurj.1506954

Received: June 29, 2024
Accepted: August 22, 2024
Published Online: August 25, 2024

molecules working in this pathway. With this abnormal expression, the transcription of genes that cause various diseases and cancers takes place [3, 5, 6]. With this activation, both the transcription of proteins working in the signaling pathway takes place and the transcription control of many genes that play an important role in proliferation, cell cycle and differentiation processes is provided [7, 8]. T Cell Factor 7 Like 2 (TCF7L2) and Lymphoid Enhancer Factor-1 (LEF-1) is a family of DNA-binding transcription factors and an important component of β-catenin-mediated gene regulation [9]. Wnt signaling is thought to be effective through interactions between β-catenin and members of the transcription factors LEF-1/TCF7L2 family. LEF-1/TCF7L2 transcription factors mediate a nuclear response by Wnt signals by interacting with β-catenin. Other cellular events that increase the stability of the Wnt signal and β-catenin lead to transcriptional activation with β-catenin and LEF-1/TCF7L2 proteins. In the absence of Wnt signaling, LEF-1/TCF7L2 proteins suppress transcription. LEF-1/TCF7L2 transcription factors can also interact with other cofactors and play a role in the assembly of multiple protein enhancing complexes, which may allow the integration of multiple signal transducing pathways. Stabilized β-catenin translocates into the nucleus, binds to LEF-1/TCF7L2 factors, and regulates interactions between LEF-1/TCF7L2 and nucleus suppressor proteins, a process that activates Wnt target genes [10]. TCF7L2 regulates the expression of genes required for embryo implantation via the Wnt/β-catenin signaling pathway. In this process, it controls critical biological events such as proliferation, differentiation, and migration of cells. The function of TCF7L2 is crucial for successful implantation. Therefore, disruption of these mechanisms may be associated with implantation failure, miscarriage, or other reproductive disorders [10].

Implantation of blastocyst in rats, i.e. placement, binding and subsequent invasion of the trophoblast into the uterine lumen epithelium, is an important process that requires complex biological communication between fetal and maternal tissues. One of the most critical factors for implantation is that blastocyst activation is synchronized with uterine receptivity; the other is controlled by ovarian steroid hormones [11]. In rats, estrogen is essential for proliferation and differentiation of the luminal and glandular epithelium of the uterus, while the coordinated action of estrogen and progesterone promotes stromal cell differentiation. Although the factors driving blastocyst activation are not yet fully understood, various signaling molecules that prepare the uterus for blastocyst implantation are thought to be cell transcription factors [11]. Considering that Wnt signaling plays an important role in embryonic development, it may not be surprising that this particular pathway plays a role in blastocyst activation, implantation, and decidualization as well as uterine growth in mice [12]. Studies have also shown that estrogen upregulates the β-catenin-dependent transcription factors TCF7L2 and LEF-1 independently of the estrogen receptor [13]. Interestingly, hormones trigger the physical interaction of ERa with activated LEF-1/TCF7L2-3 and this interaction directs it to target genes dependent on estrogen and Wnt signaling, suggesting that cross-talk between estrogen and Wnt may be critical for endometrial functions [13]. The attachment of blastocyst has been shown to induce TCF7L2/β-catenin-dependent signaling in circular smooth muscle cells of the myometrium and in the uterine epithelium at the implantation site [14].

In this study, we used immunofluorescence staining method to reveal the function of TCF7L2, LEF-1 proteins in tissues in the estrus cycle in the rat endometrium. Our results suggest that cell transcription plays a central role in coordinating the uterine-embryo interactions required for implantation of TCF7L2 and LEF-1 with the luminal epithelium at the site of possible implantation.

METHODS

Experimental Groups

For this study, 5 adult female Wistar albino rats, 6-8 weeks old and weighing between 220 and 250 grams, were obtained from the Animal Laboratory of Cumhuriyet University (Sivas, Turkey). The animals used in the study were the group in which a normal estrous cycle was provided at room temperature, with 12-hour light-12-hour dark periods, without pregnancy. The animals considered to have entered a normal estrous cycle were given 3 mg/kg Xylazine HCL + 90 mg/kg Ketamine HCL intraperitoneally on the 1st, 2nd, 3rd and 4th days (diestrous, proestrous, estrous, metaestrous) after the 5th day and for all animals every day, and the uterine tissues were taken under anesthe-

sia with appropriate methods for examination. Routine follow-up protocols were applied for immunofluorescence examinations to demonstrate LEF and TCF7L2 proteins. Sections taken for microscopic evaluation were evaluated using an Olympus BX51 (Japan) brand microscope and photographs were taken from appropriate areas.

Tissue Preparation

Uterine tissues taken after euthanasia were fixed in 10% buffered neutral formalin for at least 48 hours and in 4% paraformaldehyde at +4 degrees for 24 hours. After dehydration with increasing grades of ethanol using a tissue tracking device, they were cleared with xylene and blocked in paraffin.

Immunofluorescence Staining Protocol

After the 3-4 µm serial sections taken from the tissue samples embedded in paraffin were kept in the oven for 1 night, deparaffinization was performed in Xylol. Epitopes were released in 10 mM sodium citrate buffer (pH=6) at maximum power and 550W, respectively, in the microwave oven twice for 5 minutes. Pappen (Daido Sangyo Co., Ltd. Tokyo, Japan). The sections were washed in washing solution (PBS-Triton X-100) twice for 3 minutes. The sections were incubated in SuperBlock (Sky Tech Lab, USA) solution at room temperature for 30 minutes to prevent nonspecific transport of immunoglobulin. (Serum Blocking). The sections were incubated overnight with primary antibodies in a humid dark environment at TCF7L2 and LAEF-1 +4 degrees. It was washed in washing solution (PBS-Triton X-100) 4 times for 3 minutes each. Secondary antibody Goat Anti-Rabbit IgG H&L (Alexa Flour 488): ab150077 abcam) was incubated at room temperature for 1 hour in a humid environment. It was washed in washing solution (PBS-Triton X-100) 4 times for 3 minutes each. Core staining was performed with 0.5 ug/ml DAPI (Sigma, USA) at room temperature for 10 minutes. It was washed in washing solution (PBS-Triton X-100) for 5 minutes. The closure was done with the closure medium.

RESULTS

Preparations prepared following routine protocols were stained with hematoxylin-eosin in the first stage and then examined under a light microscope. In the second stage, immunofluorescent stains containing LEF-1 and TCF7L2 antibodies were applied to the preparations.

Estrous Cycle (Hematoxylin-Eosin)

Proestrous phase

It was observed that the lumen was filled with fluid. It was determined that mitotic activity continued in the epithelial cells consisting of single-layered columnar cells. In the following process, it was observed that the columnar cells gradually increased in size and transformed into single-layered high columnar cells (Fig. 1. G and H)

Estrous phase

In light microscopic examinations, it was observed that the uterine lumen distension reached the maximum level. In aoddition, a significant difference in size was

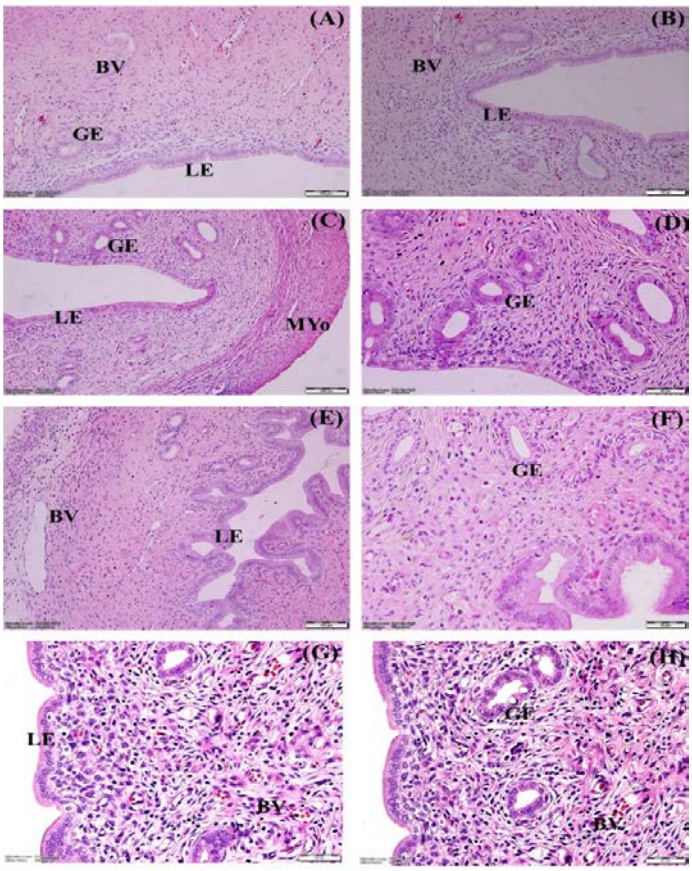


Fig. 1. Estrous cycle stages: Proestrus (G-H), Estrus (E-F), Metaestrus (C-D), Diestrus (A-B). UL=uterine lumen, UE=uterine epithelium, BE=gland epithelium, L=leukocyte, KD=blood vessel.

Table 1. TCF7L2 and LEF-1 immunolocalizations in estrous cycle stages

Protein	Endometrial region\Estrous cycle	Proestrous	Estrous	Metaestrous	Diestrous
LEF-1	PMC	-	++	++	+
	Myometrium	-	++	+	-
	Luminal Epithelium	++	+++	+	+
	Glandular Epithelium	No gland	No gland	+++	++
	Endometrial basal stroma	+	++	++	+
	Blood vessel	++	+++	++	+
TCF7L2	PMC	+++	+++	++	++
	Myometrium	+	+	++	++
	Luminal Epithelium	+	-	-	-
	Glandular Epithelium	No gland	No gland	+++	-
	Endometrial basal stroma	++	+++	++	+++
	Blood vessel	++	++	+++	+++

TCF7L2=T Cell Factor 7 Like 2, LEF-1=Lymphoid Enhancer Factor-1, PMC= Perimetrial myometrial area

detected in the uterine epithelial cells arranged in clusters. No leukocytes were found in the uterine preparations in the estrus stage (Fig. 1. E and F)

Metaestrous phase

While luminal epithelium and gland vacuolar degenerations continued, mitotic activity was observed to have started again. In addition, dominant leukocytes were observed in metaestrus. A decrease was observed in blood vessels and gland epithelium (Fig 1. C and D).

Diestrous phase

The uterus has cuboidal-prismatic epithelial cells. In this stage, the lumen of the uterus is observed to expand. In the uterus in dietrus, the epithelial cells have atrophic and collapsed features. While sparse degenerative cells are observed in the endometrial glands, stromal edema is detected in the stroma region. It has been determined that endometrial regeneration has started again (Fig 1. A and B).

Expression of LEF-1 and TCF7L2 during Estrous Cycle Stages

This group estrous cycle was examined in 4 basic stages (diestrous, proestrous, estrous and metaestrous) based on histological findings. Immunofluorescent dyes containing LEF-1 and TCF7L2 antibodies were applied to the preparations prepared following routine protocols, and the immunolocalization levels of these molecules in perimetrial-myometrial connective tissue, myometrium, uterine epithelium, gland epithelium, stroma, and blood vessels were examined under an immunofluorescent microscope. cake is shown in Table 1.

Proestrous

TCF7L2 molecule was expressed in all regions in the proestrus phase, which constitutes the 1st stage of the estrus cycle (Fig. 2. C and D). The most localization occurred in the perimetrial myometrial region (Fig. 2. C). Blood vessels showed a moderate immune reaction in the form of endothelials. The lowest level of expression belongs to the luminal epithelium. Immunolocalization levels of the LEF-1 molecule were observed in the highest endometrial basal stroma region. No localization was observed in the myometrium and perimetrial myometrial area. The expression level of the luminal epithelium was expressed as strong (Fig. 2. A and B).

Estrous

While estrous shows strong expression in TCF7L2, perimetrial myometrial area and endometrial basal stroma in the estrus stage, there is no expression in the luminal epithelium (Fig. 3. C). While LEF-1 was strongly immunolocalized in endothelials, TCF7L2 showed moderate expression (Fig. 3. A). The

highest localization of LEF-1 was observed in the luminal epithelium (Fig. 3. B).

Metaestrous

Uterine epithelium showed the least immunoreactivity compared to almost all stages of the estrous cycle, while strong localization was observed in the gland epithelium areas. Very little expression was observed in the endometrial basal stroma areas compared to the subluminal stromal regions (Fig. 4. A, B, C and D). It was observed in the metaestrus phase in the gland epithelial areas where LEF-1 protein was most expressed throughout the estrous cycle (Fig. 4. A and B). The TCF7L2 molecule is not localized in the uterine epithelium (Fig. 4. C and D). Moderate immunolocalization occurred in the endometrial basal stroma. While moderate strong expression was observed in blood vessels in certain areas, unlike other molecules, moderate strong localization was observed in perimetrial myometrial connective tissue areas. The level of immunolocalization of TCF7L2 along the myometrium-endometrium border is moderate.

Diestrous

Poor expression was observed in the uterine epithelium, gland epithelium, subluminal stroma and endometrial basal stroma of LEF-1. In the blood vessels and blood vessel stroma, the expression is quite weak in the same way (Fig. 5. A and B). Localization of the molecule in the perimetrial-myometrial connective tissue region is poor. The TCF7L2 molecule, on the other hand, is not expressed in the cytoplasm of the uterine epithelium (Fig. 5. C). It has been determined that TCF7L2 shows strong expression in blood vessels (Fig. 5. D). It was determined that only TCF7L2, one of the signaling pathway molecules, was expressed in the perimetrial-myometrial connective tissue area of the uterus, and the localization intensity was moderate. Similarly, immunolocalization of the molecule in the myometrium region occurred at a moderate level (Fig. 5. C).

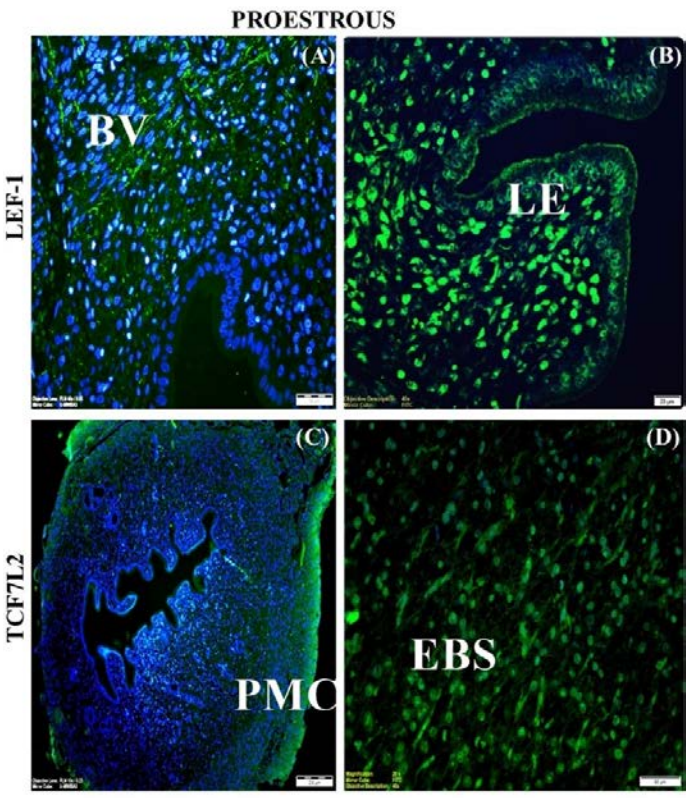


Fig. 2. Immunolocalization of LEF-1 and TCF7L2 in the proestrus phase. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma.

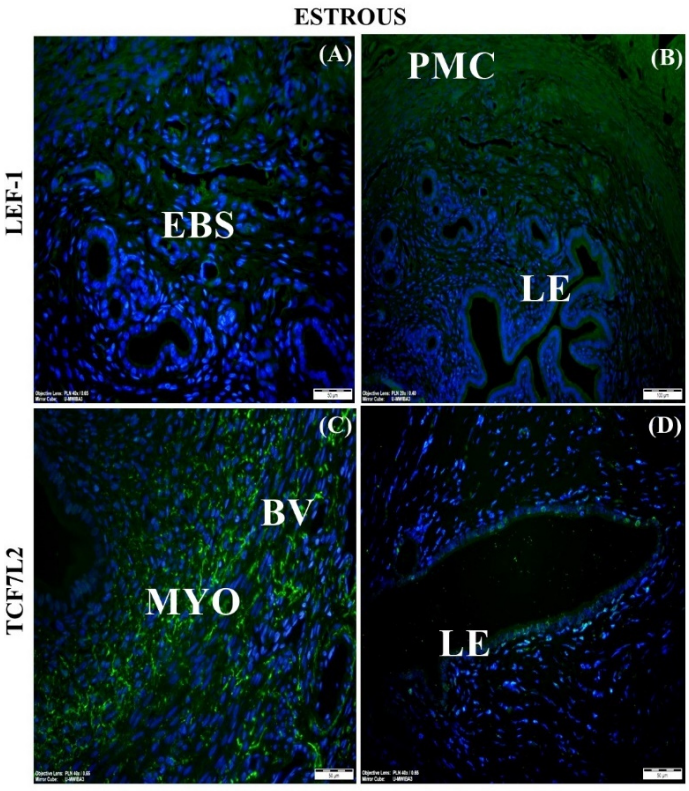


Fig. 3. Immunolocalization of LEF-1 and TCF7L2 in the estrus stage. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma, MYO=Myometrium.

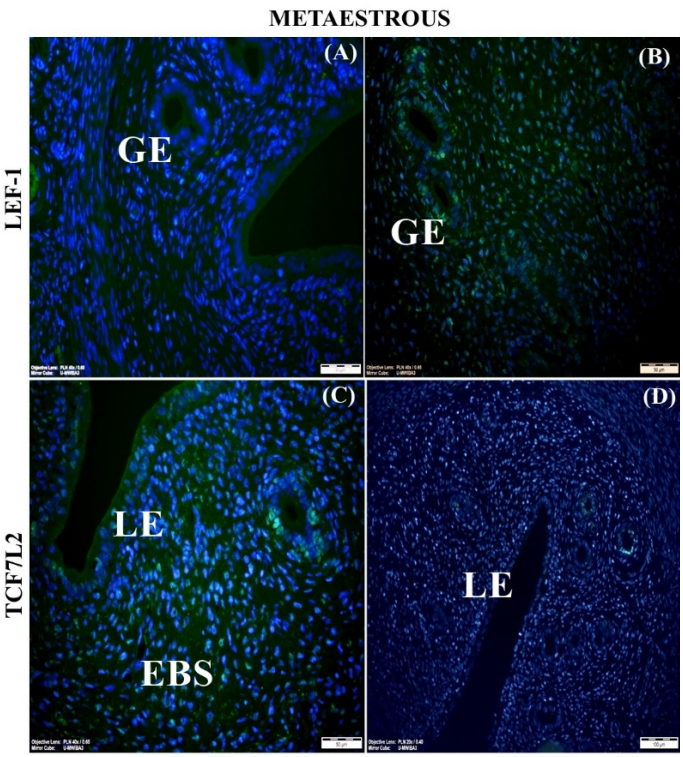


Fig. 4. Immunolocalization of LEF-1 and TCF7L2 in the metaestrus phase. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma, GE=Gland Epithelium.

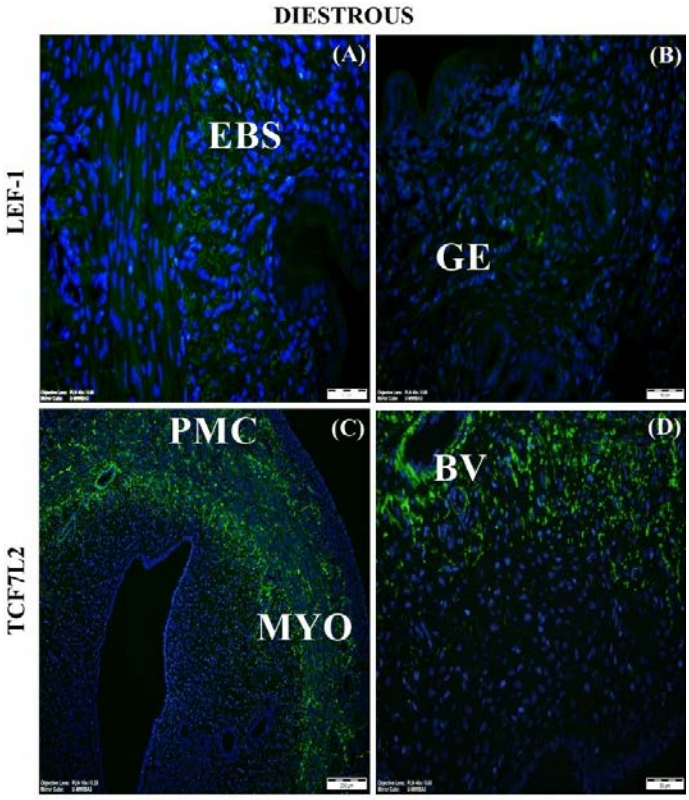


Fig. 5. Immunolocalization of LEF-1 and TCF7L2 in the diestrus phase. BV=Blood vessel, LE=Luminal epithelium, PMC=Perimetrial myometrial area, EBS=Endometrial basal stroma, MYO=Myometrium.

DISCUSSION

Although the embryo-uterine interaction is known to play an important role in facilitating implantation, it is known that several signaling pathways are specifically activated in the uterus in response to signals secreted by the blastocyst. Our results show that blastocyst activates the Wnt-dependent β-catenin signal in the uterine endometrium and activation of this pathway is necessary for implantation. These findings suggest that this paracrine signaling mechanism plays a central role in coordinating the uterus-embryo interactions required for implantation.

The TCF7L2 molecule is a Wnt/beta-catenin-dependent protein. Binding of the Wnt/protein to the receptors initiates signal transmission in the cell membrane and causes the disintegration of the destructive complex present in the cytosol. As a result of the dispersion of this chemical complex, the β-catenin, which is freed from the phosphorylation effect, is introduced into the nucleus, where a direct signal is transmitted from the cytoplasm to the nucleus [15]. Biomolecules involved in the nuclear activation of the Wnt/β-catenin signaling pathway were identified as TCF7L2)/LEF-1 transcription factors. This mechanism is explained as follows: TCF7L2 transcription factors are found in the nucleus and bind to DNA and activate gene transcription. Therefore, they are vital in many cellular processes [16]. The C-terminal ends of TCF7L2/LEF-1 transcription factors have a DNA binding site consisting of the sequence "AGATCAAAGGG" that can bind to a specific region of DNA [17]. This area is called high-mobility group (HMG). In the nucleus, these transcription factors need to bind to the β-catenin protein in order to be activated. Therefore, β-catenin is known to be a coactivator of TCF7L2/LEF transcription factors [18, 19]. The structure formed by this binding of beta-catenin is called "β-catenin-TCF7L2/LEF1 transcription complex" and it has been determined that this complex will

bind to DNA to form target genes [20, 21]. In a study conducted in 2007, the working mechanism of TCF7L2/LEF transcription factors argues that while the signaling pathway of Wnt beta-catenin is inactive, the transcription factors should also be inactive. He said that beta-catenin, which is broken down by the destructive complex effect that is active when the signal pathway is inactive, cannot enter the nucleus and cannot activate them because beta-catenin cannot enter the nucleus and cannot bind to transcription factors. As a result, it has been stated that genes inhibit transcription and various other proteins such as Groucho/TLE (Transducin-like-Enhancer of split) and C-terminal binding proteins (CtBP) in the nucleus also bind to TCF7L2/LEF transcription factors [22]. This binding allows to keep transcription factors inactive. Therefore, these proteins are known as transcription inhibitors.

The TCF7L2 protein, known as the T cell factor, increases cytosolic accumulation that inhibits the degradation of β-catenin and promotes the binding of TCF7L2 family transcription factors to the lymphoid-strengthening binding factor, LEF-1 [16, 23]. In unstimulated cells, they act as transcription inhibitors in other preservatives such as Lef/TCF7L2 groucho transducin-like (TLE) family proteins [24]. Together with these properties, these receptors provide an activation site for TCF7L2/LEF upon WNT activation. Cyclin, which is involved in active TCF7L2/LEF cell proliferation and invasion, induces the expression of target genes such as D1 [16]. Pollheimer *et al*. [25] associated it with the synthesis of TCF7L2 or TCF7L2-4 in the formation and differentiation of extravillus trophoblasts or trophoblasts [25]. Regardless of these studies, in our studies on rat endometrium, the moderate and strong immune reaction of rats in all four stages throughout the estrus cycle, especially in the endometrial basal stroma areas, supported the presence of a transcription in the nuclei of the cells located here, but the fact that it is not localized in the uterine epithelium in the estrus, metaestrus and diestrus periods suggested that factors that are not yet known may be effective. The staining of the TCF7L2 molecule in the nucleus rather than in the cytoplasm shows that it is a transcription in the nucleus, and it is thought that this result may be due to the differentiation in the nuclei of the decidual cells. LEF, on the other hand, initiates the recognition of the wnt ligand with transmembrane receptors on the cell surface and the cascade that will redirect it to the nucleus by stabilizing the normally unstable armadillo repeat protein, beta catenin. The Lef protein interacts with the Lef/TCF7L2 DNA binding protein in the beta-catenin nucleus, which has increased stabilization and amount in the cell depending on the canonical wnt signal with the TCF7L2 protein [2]. In a study on LEF-1 protein and endometrial carcinomas, mutations of the CTNNB1 gene that occur in 12-25% of endometrial carcinomas have typically shown that beta-catenin causes an increase in cytoplasmic and nuclear accumulation, which subsequently leads to activation of LEF-1 and TCF7L2 family members. This relationship between activated LEF-1 protein and mutated beta-catenin has given a clue that LEF-1 may cause irregularity of molecules in endometrial cancer cases [2, 26]. Wnt suggests that beta-catenin will contribute to the regulation of uterine growth on LEF-1 of the signaling pathway, as well as to the normal development and function of the uterus [27]. In a study by Shelton *et al*. [28] on endometrial gland formation in mice, they observed that LEF-1 protein may be expressed during uterine development and estrus period. They reported that the Lef/TCF7L2-dependent signaling of the LEF-1 expression Wnt/beta-catenin signaling pathway during uterine development had a delicate regulation during the estrous cycle in mice. They observed that there may be changes in cell proliferation in the glands during the estrous cycle. In the same study, they showed that the expression of LEF-1 in the uterus was effective in both the development and the formation and control of the endometrial glands, and in the absence of LEF-1, despite the presence of a normal endometrium, it resulted in the formation of an unsuccessful uterine gland. When knockout was characterized in the LEF-1 study in mice, it was shown that these mice lacked mammary glands and epithelial mesenchymal interactions, for example, in hair follicles [29]. There have not been many studies on the presence of LEF-1 in estrus and its period, but it is known that LEF-1 is a beta-catenin-dependent transcription factor in the Wnt signaling pathway. During estrus cycle periods, LEF-1 protein was expressed at the same level in almost all stages. It has been confirmed that the estrous cycle is effective in the development of the glandular gland, especially

during the metaestrus period, by being expressed in the glandular epithelium. It was thought that immunolocalization in the gland epithelium during the metaestrus period may be due to the variability of progesterone and LH levels. In the literature, it is observed that it helps the development of the uterine gland and that the estrous cycle is mostly expressed during the proestrus period, and the observed LEF-1 protein gains accuracy by helping the development of the gland with our findings, but it does not coincide with the stronger immune reaction of the gland epithelium in the metaestrus of the estrous cycle compared to the proestrus period.

CONCLUSION

It can be concluded that TCF7L2 and LEF-1 work together in the Wnt/β-catenin signaling pathway to regulate the cellular and genetic processes required for the successful implantation of the embryo into the uterine wall, and therefore the interaction of these molecules plays a critical role in the success of implantation. As a result, it is seen that the transcription in the cell nucleus occurs by beta-catenin-dependent TCF7L2/LEF-1 proteins for successful implantation and the development of the uterine epithelium and uterine glandular glands.

Authors' Contribution

Study Conception: TD; Study Design: TD; Supervision: TD; Funding: TD; Materials: TD; Data Collection and/or Processing: TD; Statistical Analysis and/or Data Interpretation: TD; Literature Review: TD; Manuscript Preparation: TD and Critical Review: TD.

Ethics Approval

This study was approved by the Sivas Cumhuriyet University Animal Experiments Local Ethics Committee (Decision no.: 12, Date: 27.01.2017)

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Kaloğlu C, Gürsoy E, Onarlioğlu B. Early maternal changes contributing to the formation of the chorioallantoic and yolk sac placentas in rat: a morphological study. Anat Histol Embryol. 2003;32(4):200-206. doi: 10.1046/j.1439-0264.2003.00450.x.
2. Dağdeviren T. Peri-implantasyon döneminde sıçan endometriumunda wnt-β katenin yolağının TCF, lef ve caspase-9 ekspresyonundaki rolü. 2019.
3. Nusse R. Wnt signaling in disease and in development. Cell Res. 2005;15(1):28-32. doi: 10.1038/sj.cr.7290260.
4. Miller JR, Hocking AM, Brown JD, Moon RT. Mechanism and function of signal transduction by the Wnt/beta-catenin and Wnt/Ca2+ pathways. Oncogene. 1999;18(55):7860-7872. doi: 10.1038/sj.onc.1203245.
5. Polakis P. Wnt signaling and cancer. Genes Dev. 2000;14(15):1837-1851.
6. Moon RT, Kohn AD, De Ferrari GV, Kaykas A. WNT and beta-catenin signalling: diseases and therapies. Nat Rev Genet. 2004;5(9):691-701. doi: 10.1038/nrg1427.
7. Miller JR. The Wnts. Genome Biol. 2002;3(1):REVIEWS3001. doi: 10.1186/gb-2001-3-1-reviews3001.
8. Mikels AJ, Nusse R. Wnts as ligands: processing, secretion and reception. Oncogene. 2006;25(57):7461-7468. doi: 10.1038/sj.onc.1210053.
9. Panhuysen M, Vogt Weisenhorn DM, Blanquet V, et al. Effects of Wnt1 signaling on proliferation in the developing mid-/hindbrain region. Mol Cell Neurosci. 2004;26(1):101-111. doi: 10.1016/j.mcn.2004.01.011.
10. Eastman Q, Grosschedl R. Regulation of LEF-1/TCF transcription factors by Wnt and other signals. Curr Opin Cell Biol. 1999;11(2):233-240. doi: 10.1016/s0955-0674(99)80031-3.
11. Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. Nat Rev Genet. 2006;7(3):185-199. doi: 10.1038/nrg1808.
12. Chen Q, Zhang Y, Lu J, et al. Embryo-uterine cross-talk during implantation: the role of Wnt signaling. Mol Hum Reprod. 2009;15(4):215-221. doi: 10.1093/molehr/gap009.
13. Shiina H, Igawa M, Breault J, et al. The human T-cell factor-4 gene splicing isoforms, Wnt signal pathway, and apoptosis in renal cell carcinoma. Clin Cancer Res. 2003;9(6):2121-2132.
14. Mohamed OA, Jonnaert M, Labelle-Dumais C, Kuroda K, Clarke HJ, Dufort D. Uterine Wnt/beta-catenin signaling is required for implantation. Proc Natl Acad Sci U S A. 2005;102(24):8579-8584. doi: 10.1073/pnas.0500612102.
15. Komiya Y, Habas R. Wnt signal transduction pathways. Organogenesis. 2008;4(2):68-75. doi: 10.4161/org.4.2.5851.
16. Willert K, Jones KA. Wnt signaling: is the party in the nucleus? Genes Dev. 2006;20(11):1394-1404. doi: 10.1101/gad.1424006.
17. Mulholland DJ, Dedhar S, Coetzee GA, Nelson CC. Interaction of nuclear receptors with the Wnt/beta-catenin/Tcf signaling axis: Wnt you like to know? Endocr Rev. 2005;26(7):898-915. doi: 10.1210/er.2003-0034.
18. Graham TA, Weaver C, Mao F, Kimelman D, Xu W. Crystal structure of a beta-catenin/Tcf complex. Cell. 2000;103(6):8858-96. doi: 10.1016/s0092-8674(00)00192-6.

19. Chen X, Yang J, Evans PM, Liu C. Wnt signaling: the good and the bad. Acta Biochim Biophys Sin (Shanghai). 2008;40(7):577-594. doi: 10.1111/j.1745-7270.2008.00440.x.
20. Lustig B, Behrens J. The Wnt signaling pathway and its role in tumor development. J Cancer Res Clin Oncol. 2003;129(4):199-221. doi: 10.1007/s00432-003-0431-0.
21. Xu W, Kimelman D. Mechanistic insights from structural studies of beta-catenin and its binding partners. J Cell Sci. 2007;120(Pt 19):3337-3344. doi: 10.1242/jcs.013771.
22. Carl M, Bianco IH, Bajoghli B, Aghaallaei N, Czerny T, Wilson SW. Wnt/Axin1/beta-catenin signaling regulates asymmetric nodal activation, elaboration, and concordance of CNS asymmetries. Neuron. 2007;55(3):393-405. doi: 10.1016/j.neuron.2007.07.007.
23. Hoppler S, Kavanagh CL. Wnt signalling: variety at the core. J Cell Sci. 2007;120(Pt 3):385-93. doi: 10.1242/jcs.03363.
24. Buscarlet M, Stifani S. The 'Marx' of Groucho on development and disease. Trends Cell Biol. 2007;17(7):353-361. doi: 10.1016/j.tcb.2007.07.002.
25. Pollheimer J, Loregger T, Sonderegger S, et al. Activation of the canonical wingless/T-cell factor signaling pathway promotes invasive differentiation of human trophoblast. Am J Pathol. 2006;168(4):1134-1147. doi: 10.2353/ajpath.2006.050686.
26. Machin P, Catasus L, Pons C, Muñoz J, Matias-Guiu X, Prat J. CTNNB1 mutations and beta-catenin expression in endometrial carcinomas. Hum Pathol. 2002;33(2):206-212. doi: 10.1053/hupa.2002.30723.
27. Tulac S, Nayak NR, Kao LC, et al. Identification, characterization, and regulation of the canonical Wnt signaling pathway in human endometrium. J Clin Endocrinol Metab. 2003;88(8):3860-3866. doi: 10.1210/jc.2003-030494.
28. Shelton DN, Fornalik H, Neff T, et al. The role of LEF1 in endometrial gland formation and carcinogenesis. PLoS One. 2012;7(7):e40312. doi: 10.1371/journal.pone.0040312.
29. van Genderen C, Okamura RM, Fariñas I, et al. Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in LEF-1-deficient mice. Genes Dev. 1994;8(22):2691-2703. doi: 10.1101/gad.8.22.2691.

RETRACTION NOTE:
This study has been retracted at the author's request

The European Research Journal 2024;10(6):626-633 Review

DOI: https://doi.org/10.18621/eurj.1476615 *Healthcare*

The significance of personalized medicine in healthcare services of the 21st century: a brief literature review

Ebru Uğraş Tiryaki

Mamak District Health Directorate, Ankara, Türkiye

ABSTRACT

In modern healthcare services, patient safety is a primary goal. With technological advancements, the complexity of healthcare services increases, which in turn creates increased pressure on health professionals during decision-making processes and can lead to errors worldwide. Communication gaps, human factors, patient-originated issues, technical failures, and inadequate policies have been identified as the main causes of medical errors. While research shows that errors stem from human nature and are inevitable, it is emphasized that it is possible to develop methods that enhance patient safety. Utilizing digital technologies to improve the quality and efficiency of healthcare services is a crucial strategy. Innovations such as wearable technologies, mobile devices, digital media-delivered education and consulting services, telehealth applications, 3D printers, clinical decision support systems, and implantable biosensors encompass advancements in the digital health field. This research aims to analyze the complex and dynamic structure of healthcare services in the 21st century, especially considering the opportunities presented by the integration of artificial intelligence and genomic data, within the scope of the relevant literature.

Keywords: Personalized medicine, 21st century, healthcare services, patient safety

According to the World Health Organization (WHO), the complexity of health systems can lead to patient harm, constituting a violation of patient safety [1]. Patients can face fatal consequences that become permanent if systematic measures are not taken to prevent errors in medical settings [2].

The Ministry of Health is the primary institution responsible for policy formation and the delivery of health services in Turkey [3]. It was established on May 3, 1920, following the inauguration of the Grand National Assembly of Turkey with Law No. 3. Despite the challenges of the war years from the 1920s to 1923, the state managed to provide health services through municipal and quarantine doctors, small health officials, 86 treatment facilities, 6,437 patient beds, 554 doctors, 69 pharmacists, 4 nurses, 560 health officers, and 136 midwives by 1946. The "First Ten-Year National Health Plan" introduced in 1946 never came into effect due to administrative changes. The continuation of this plan was the "National Health Program and Health Bank Studies" announced on December 8, 1954. This program aimed to increase the number of doctors and other health workers by dividing the country into seven health regions and estab-

Corresponding author: Ebru Uğraş Tiryaki, MD.,
Phone: +90 312 369 69 95, E-mail: ebruugras@hotmail.com

How to cite this article: Uğraş Tiryaki E. The significance of personalized medicine in healthcare services of the 21st century: a brief literature review. Eur Res J. 2024;10(6):626-633. doi: 10.18621/eurj.1476615

Received: May 1, 2024
Accepted: June 23, 2024
Published Online: July 16, 2024

lishing medical faculties in each. For example, following the medical faculties of Istanbul and Ankara Universities, Ege University Faculty of Medicine began training students in 1955. Compared to 3,020 doctors in 1950, there were 8,214 doctors by 2016 [4, 5]. The number of other health workers (nurses, midwives) also significantly increased. Along with the health services provided, the number of hospitals and health facilities grew, and there were decreases in the prevalence of some diseases and in infant mortality rates [6, 7]. Legislation regulating civil society groups, including the Turkish Medical Association, pharmacies, nursing, and the Turkish Pharmacists' Association, was also established, culminating in the Socialization of Health Services Law No. 224 in 1961. The true socialization of health began in 1963 and was fully implemented in 1983 with the help of state, district, and provincial hospitals [8].

In 1989, the decree-law established the "Ministry of Health and Social Assistance" replacing the "Health Ministry". Primary health services are provided by the Health Ministry through health centers, maternal and child health and family planning centers, tuberculosis dispensaries, malaria centers, and cancer fighting centers [9, 10]. Secondary and tertiary services are provided by the Health Ministry along with other public institutions, foundations, and commercialized health services. Notably, the Health Transformation Program in 2003 marked the ministry's shift to a "planning and supporting" role. The eight themes of the Health Transformation Program are as follows: (1) Planning and steering by the Ministry of Health, (2) An all-encompassing general health insurance system, (3) Accessible, affordable, and welcoming health services (to support system institutions with education and science, Quality and accreditation for competent and effective health services, Institutional structuring in rational drug and material management), (4) Highly motivated health workforce equipped with knowledge and skills, (5) Education and science to support system institutions, (6) Quality and accreditation for competent and effective health services, (7) Institutional structuring in rational drug and material management, (8) Effective information access in decision-making: Health information system. In 2007, three additional headings were added: (1) Health improvement and healthy life programs for a better future, (2) multi-sectoral health responsibility for activating stakeholders and inter-sectoral collaboration, (3) Transboundary health services to enhance the country's strength internationally [11].

Personalized writing techniques can avoid medical errors and enhance patient safety. Personalized medicine practices can be seen as a significant advancement in preventive and evidence-based health systems. Most medical procedures today are designed for the average person accepted by most of the population. However, each person is unique with a different genetic makeup, which explains why some patients respond positively to a treatment regimen that fails in others. Researchers have identified genetic variations in patients' responses to targeted therapies and developed diagnostic tests based on genetic or other molecular causes. This innovative approach to disease prevention and treatment focuses on tailoring health services to everyone’s genetic makeup, environmental factors, and personal characteristics [12, 13].

HEALTHCARE SERVICES IN THE 21ST CENTURY

Since the 1960s, genetics has become an integral part of the health system and now plays a primary role in the prevention and treatment of common chronic diseases such as cancer and heart disease [14]. Renato Dulbecco realized in 1985 that sequencing the human genome was essential for advancing cancer research [15]. The Human Genome Project was initiated in 1990, with its first draft published in 2001 and the final draft in 2003 [16]. The concept of personalized medicine was first introduced to the public in a 1999 Wall Street Journal article titled "The New Age of Personalized Medicine: Targeting Drugs to Unique Genetic Profiles." This article discussed how even the best treatments in contemporary pharmacotherapy were effective in only 50-70% of patients, indicating that this method was acceptable for all individuals [16, 17].

Developments in biomedical, social, technological, and economic disciplines are believed to be the driving force behind personalized medicine. This strategy is based on finding genetic, epigenomic, and clinical information, including methods to determine how an individual's genomic profile makes them susceptible to certain diseases [18].

Standard treatments like chemotherapy and radio-

therapy do not have the same effect across all patient populations due to the heterogeneity of diseases. It is believed that personalized medical practices, by revealing individual biological distinctions, will significantly contribute to the detection and treatment of cancer [19]. The identification of individual risk factors based on genetic or physiological biomarkers for cardiovascular diseases such as atherosclerosis, heart failure, and hypertension, and the development of personalized medicine techniques are crucial for early intervention [20]. Diabetes mellitus is characterized by significant heterogeneity in genetic risk factors, underlying pathogenic mechanisms, and clinical symptoms, making it a complex and diverse disease of the endocrine system. However, individual characteristics that can influence clinical outcomes and therapeutic responses in patients with type 2 diabetes are rarely considered, and comparable treatment approaches are often utilized [21].

Personalized drug applications in managing disorders where genetic and environmental factors play a significant role can facilitate the development of targeted treatments [22, 23].

Another promising area for personalized medicine applications is dermatological diseases, which are among the most common and preventable diseases affecting millions. Personalized medicine practices can reduce side effects that may jeopardize patient safety, increase patient compliance, and provide economic benefits through the prevention, early diagnosis, and treatment processes of dermatological disorders [13]. Pain management is a very important aspect of patient safety that is considered. While everyone's pain threshold varies, basic pain management approaches are predominantly used worldwide. A study in the United States on post-surgical pain treatment suggested the use of personalized methods to create individualized pain management treatment plans based on each patient's genetic coding for analgesic metabolism and pain sensitivity [24].

Another area of interest in personalized medicine for patient safety is the development of specific protective and treatment techniques for allergy and asthma patients [25]. The synthesis of specific Immunoglobulin E (IgE) is identified as a feature of an allergic response defined by exposure to allergens and the immunological reactions to these antigens [26]. Allergic diseases, being among the most common diseases worldwide and having rapidly increased in prevalence to date, are likened to a black hole consuming resources in the medical community. Each allergic patient has unique characteristics managed by clinical history, response to treatment, cellular mechanisms, and hereditary and epigenetic control by the environment. Key terms in this field aiming to improve patient care and create better prevention and treatment strategies through phenotyping, genotyping, therapy, and biomarkers include characterizing unique features of allergy phenotypes to develop targeted allergen immunotherapy, which can improve patient safety, enhance quality of life, and provide financial benefits [27, 28].

Personalized drug procedures, although now expensive for individual patients, have the potential to minimize long-term expenditures by providing prevention methods that reduce morbidity, more accurate diagnoses, and more successful treatment regimens. Thus, scientific evidence about disease pathophysiology and genetic risk factors can be used to design a more efficient drug production method and potentially provide greater benefits to the pharmaceutical and medical device industries. Additionally, personalized medicine facilitates the provision of excellent care with highly reliable diagnostic and treatment options, enhances patient safety, and increases patient satisfaction [13, 17].

Achieving desired outcomes in personalized health applications requires successful collaboration with stakeholders. Primary stakeholders in this endeavor include service providers, service users, governments, academia, biotechnology firms, individuals/institutions working in data mining, patients, authorities, payers, and health professionals with authority over ethical regulations and legal requirements [29]. Personalized medicine practices have the potential to enhance patients' quality of life, life expectancy, and the efficient use of time and money however, it is a politically complex issue [30].

Health is a policy issue affecting numerous fields including science, technology, economics, law, and public administration. Research in Europe and the United States highlights the importance of government funding for research in this field [31,32]. Identifying protective measures for individuals at risk for specific diseases and determining early intervention methods based on variables related to disease progression at the

community level are additional significant contributions this technology can make to future health policies [33, 34].

One of the benefits of next-generation technologies for patient safety is the provision of a large amount of monitoring-based data. By analyzing this data, future health policy decisions can be informed. Future applications of personalized medicine will provide new sources of information about diagnostic and treatment options, allowing patients to have more control over their health in various ways; reliable information will be easily accessible; multidisciplinary clinical decision support systems will be used more effectively; education for health professionals will be enhanced, and resources will be more effectively used for the benefit of the community. The more precise, reliable, systematic use of data flows is expected to lay the groundwork for the emergence of new professions in the health services sector [35].

In terms of patient safety, personalized medicine methods have made many positive contributions to health systems, but there are also ethical and legal concerns. One of these concerns is the cost-benefit ratio; the question is whether the expected benefits of these highly costly technologies will be realized in practice.In a world where demand is unlimited, resources are limited, and the costs of health services are rising, whether investing in personalized medicine is a cost-effective strategy is debatable [36, 37]. Equal and equitable access to these technologies, the appropriateness of revealing individuals' genetic sequences in a health sector with intense information asymmetry in terms of autonomy and privacy, and the accuracy and reliability of technologies used in the field of personalized medicine are among the other ethical issues under discussion.

METHODS

The methodology of this research has been designated as a literature review. Accordingly, the study is designed to thoroughly examine existing studies and research on precision medicine, artificial intelligence, and genomic data relevant to the objectives of the research. This process will utilize scientific databases such as PubMed, Scopus, Web of Science, and Google Scholar. Keywords include "precision medicine," "artificial intelligence in healthcare," and "genomic data and medicine." Selected articles are limited to those published in the last ten years. Accordingly, the findings section is subdivided based on the data considered.

RESULTS

Precision Medicine

The broad goal of precision medicine is to tailor treatments, drug types, and dosages to each individual while also adapting personal prevention methods, thereby enhancing patient safety [38]. When considering patient safety, issues such as drug ineffectiveness, side effects, drug interactions, and patient dissatisfaction might necessitate trial and error in treatment adjustments, potentially leading to delayed correct treatment and disease progression [39, 40]. For diseases with high burdens and mortality rates such as cancer, diabetes, neurodegenerative diseases, systemic lupus erythematosus, and rheumatoid arthritis, as well as less common diseases like infectious meningitis, encephalitis, and vasculitis, precision medicine technologies hold promise for early diagnosis and treatment [41, 42]. For example, cancer, considered a leading cause of death globally, is expected to kill approximately 35 million people by 2050, but if diagnosed early, can be effectively treated [43].

Genomic Data and Medicine

Standard treatments like chemotherapy and radiotherapy do not have uniform effects across all patient populations due to the heterogeneity of diseases. Precision medical practices that reveal individual biological distinctions are believed to significantly contribute to cancer detection and treatment [44-45]. The identification of individual risk factors based on genetic or physiological biomarkers is crucial for early intervention in cardiovascular diseases such as atherosclerosis, heart failure, and hypertension [46]. Diabetes mellitus, characterized by significant heterogeneity in genetic risk factors, underlying pathogenic mechanisms, and clinical symptoms, presents a complex and varied disease of the endocrine system. However, individual characteristics that may influence clinical outcomes and therapeutic responses in patients with type 2 diabetes are often overlooked, with frequent reliance on

comparable treatment approaches [47].

In disorders where genetic and environmental factors play a significant role, personalized drug applications can facilitate the development of targeted treatments [48]. Another promising area for precision medicine applications is dermatological diseases, which are among the most common and preventable diseases affecting millions. Personalized medicine practices can reduce side effects that may jeopardize patient safety, enhance patient compliance, and provide economic benefits through prevention, early diagnosis, and treatment processes of dermatological disorders [49].

Pain Management

Pain management is a critical aspect of patient safety. Although each individual's pain threshold varies, basic pain management approaches are predominantly used worldwide. In the United States, a study on post-surgical pain treatment recommended the use of precision methods to create individualized pain management treatment plans based on each patient's genetic coding for analgesic metabolism and pain sensitivity [50, 51].

Allergy and Asthma

Another area of interest in personalized medicine for patient safety is the development of specific protective and treatment techniques for allergy and asthma patients. The synthesis of specific Immunoglobulin E (IgE) is a feature of an allergic response defined by exposure to allergens and the resulting immunological reactions [52].

Artificial Intelligence and Precision Medicine Health Services

While personalized drug procedures are now expensive for individual patients, they hold the potential to minimize long-term expenses by providing prevention methods that reduce morbidity, more accurate diagnoses, and more successful treatment regimes. Thus, scientific evidence about disease pathophysiology and genetic risk factors can be used to design a more efficient drug production method and potentially provide greater benefits to the pharmaceutical and medical device industries in Fig. 1. Additionally, precision medicine facilitates the provision of excellent care with highly reliable diagnostic and treatment options, enhances patient safety, and increases patient satisfaction [53].

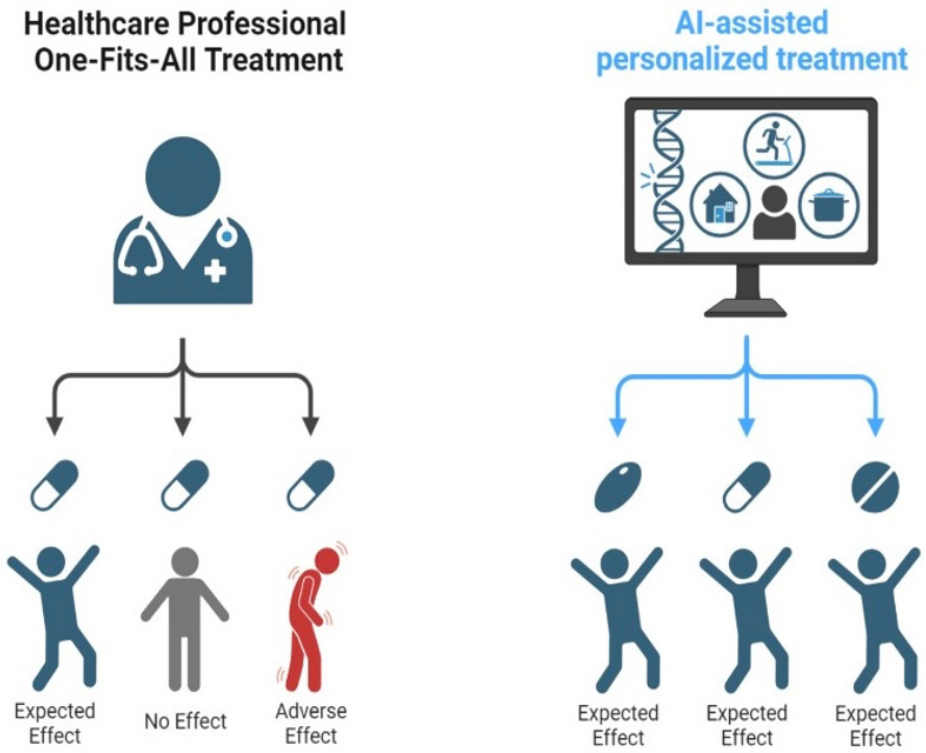


Fig. 1. Personalized Medicine AI vs Traditional Techniques (Created with BioRender.com).

Achieving desired outcomes in personalized health applications requires successful collaboration with stakeholders. Primary stakeholders in this endeavor include service providers, service users, governments, academia, biotechnology firms, individuals/institutions working in data mining, patients, authorities, payers, and health professionals with authority over ethical regulations and legal requirements. Precision medicine practices have the potential to enhance patients' quality of life, life expectancy, and the efficient use of time and money; however, it is a politically complex issue [54, 55].

DISCUSSION

Health policy impacts numerous fields including health, science and technology, economics, law, and public administration. Studies in Europe and the United States underscore the importance of government funding for research in this area [31, 32]. Identifying protective measures for individuals at risk for specific diseases and determining early intervention methods based on community-level disease progression variables are additional significant contributions this technology can make to future health policies [56].

One of the benefits of new-generation technologies in terms of patient safety is that they provide large amounts of monitoring data. Analyzing this data allows informed decisions about future healthcare policies to be made. Future applications of precision medicine will enable patients to take greater control over their health by providing new sources of information about diagnosis and treatment options. In addition, easy access to reliable information sources will be provided, multidisciplinary clinical decision support systems will be used more effectively, the training of healthcare professionals will be contributed and resources will be used more efficiently for the benefit of society. More precise, reliable, and systematic use of data streams will facilitate the emergence of new professions in the healthcare sector [24, 48].

Primary healthcare services are defined as services provided to individuals and families in the community universally accessible, with full participation, and at a cost that the community and country can afford. They are a vital aspect of both the country's health system and the overall social and economic development of the population [57].

As a result of market liberalization, private organizations in Turkey, as in the rest of the world, provide health services under state supervision. The competitive nature of markets necessitates various marketing strategies. The fact that health care is considered a human right makes it inevitable to criticize this situation. Due to the irreparable, irretrievable, and unacceptable nature of errors in service delivery, and the primary responsibility of health professionals, ethical rules make it imperative to distinguish patients from other consumers. These factors determine the health services provided. The provision of services that directly affect human health should be the basis of planned and carefully implemented marketing efforts [58].

CONCLUSION

Health is currently one of the sectors most affected by the digital revolution. Thanks to digital health technologies, there is a shift from traditional hospital-based, treatment-focused approaches to individual-centered preventive approaches. Soon, personalized medical applications will play a key role in preventing, diagnosing, and treating diseases in terms of patient safety.

Personalized medication applications are particularly promising for various unresolved, uncommon, autoimmune, and neurodegenerative disorders. Considering the generational and professional training differences between different patient demographics and health professionals in the community, assessing the challenges that might be encountered in technology usage is essential for training health professionals who will ensure patient safety and planning accordingly. It is crucial for countries to emphasize these concerns in their health strategies to improve public health and reduce costs over time.

Authors' Contribution

Study Conception: EUT; Study Design: EUT; Supervision: EUT; Funding: N/A; Materials: N/A; Data Collection and/or Processing: EUT; Statistical Analysis and/or Data Interpretation: EUT; Literature Review: EUT; Manuscript Preparation: EUT and Critical Review: EUT.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. WHO. Patient safety curriculum guide: multi-professional edition. Switzerland. Available at: https://iris.who.int/bitstream/handle/10665/44641/9789241?sequence=3. Accessed 2011.
2. WHO. Patient safety fact file. Patient Safety and Risk Management Service Delivery and Safety. Available at: https://www.who.int/news-room/photo-story/photo-story-detail/10-facts-on-patient-safety. Accessed August 26, 2019.
3. WHO. Cancer. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed February 3, 2022.
4. Alemdar DK, Aktaş YY. Medical error types and causes made by nurses in Turkey. TAF Prev Med Bull. 2013;12(3):307-314. doi: 10.5455/pmb.1-1345816200.
5. Blaus A, Madabushi R, Pacanowski M, et al. Personalized Cardiovascular Medicine Today: A Food and Drug Administration/Center for Drug Evaluation and Research Perspective. Circulation. 2015;132(15):1425-32. doi: 10.1161/CIRCULATIONAHA.114.009761.
6. Burau V, Nissen N, Terkildsen MD, Væggemose U. Personalised medicine and the state: A political discourse analysis. Health Policy. 2021;125(1):122-129. doi: 10.1016/j.healthpol.2020.10.005.
7. Carlsten C, Brauer M, Brinkman F, et al. Genes, the environment and personalized medicine: We need to harness both environmental and genetic data to maximize personal and population health. EMBO Rep. 2014;15(7):736-9. doi: 10.15252/embr.201438480.
8. Kasapoğlu A. Türkiye'de sağlık hizmetlerinin dönüşümü. Sosyoloji Araştırmaları Dergisi. 2016;19(2):131-174.
9. Cansever İH, Gökkaya D. Numune hastanelerinden şehir hastanelerine: Türkiye'de hastanelerin dünü, bugünü ve yarını. Balıkesir Sağlık Bilimleri Dergisi. 2023;12(2):425-436. doi: 10.53424/balikesirsbd.1070010.
10. Aksakal Hİ. Dr. Refik saydam önderliğinde Cumhuriyet dönemi sağlık hizmetlerini modernleştirme çabaları. Fırat Üniversitesi Sosyal Bilimler Dergisi. 2017;27(1):219-232.
11. Seçtim H. Sağlıkta Dönüşüm Programi Üzerine Bir Değerlendirme. Management and Political Sciences Review. 2019;1(1):117-133.
12. Abubakar AR, Chedi BA, Mohammed KG, Haque M. Drug interaction and its implication in clinical practice and personalized medicine. National Journal of Physiology, Pharmacy and Pharmacology. 2015;5(5):343-349. doi: 10.5455/njppp.2015.5.2005201557.
13. Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertil Steril. 2018;109(6):952-963. doi: 10.1016/j.fertnstert.2018.05.006.
14. Auffray C, Caulfield T, Griffin JL, et al. From genomic medicine to precision medicine: highlights of 2015. Genome Med. 2016;8(1):12. doi: 10.1186/s13073-016-0265-4.
15. Hood L, Rowen L. The Human Genome Project: big science transforms biology and medicine. Genome Med. 2013;5(9):79. doi: 10.1186/gm483.
16. Riley N. Out of date: genetics, history and the British novel of the 1990s. Med Humanit. 2021;47(2):201-209. doi: 10.1136/medhum-2020-012022.
17. Carlsten C, Brauer M, Brinkman F, et al. Genes, the environment and personalized medicine: We need to harness both environmental and genetic data to maximize personal and population health. EMBO Rep. 2014;15(7):736-739. doi: 10.15252/embr.201438480.
18. California State University. The reduction of surgical errors through a development of safety culture, teamwork, and communication. Available at: https://www.proquest.com/docview/860328049/abstract. Accessed 2010.
19. Krzyszczyk P, Acevedo A, Davidoff EJ, et al. The growing role of precision and personalized medicine for cancer treatment. Technology (Singap World Sci). 2018;6(3-4):79-100. doi: 10.1142/S2339547818300020.
20. Lee MS, Flammer AJ, Lerman LO, Lerman A. Personalized medicine in cardiovascular diseases. Korean Circ J. 2012;42(9):583-91. doi: 10.4070/kcj.2012.42.9.583.
21. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020;10(4):174-188. doi: 10.4103/ajm.ajm_53_20.
22. Nair SR. Personalized medicine: Striding from genes to medicines. Perspect Clin Res. 2010;1(4):146-50. doi: 10.4103/2229-3485.71775.
23. Ginsburg GS, Willard HF. Genomic and personalized medicine: VI-2. 2nd Edition. US: Academic Press; 2012.
24. Ferreira do Couto ML, Fonseca S, Pozza DH. Pharmacogenetic Approaches in Personalized Medicine for Postoperative Pain Management. Biomedicines. 2024;12(4):729. doi: 10.3390/biomedicines12040729.
25. Kucuksezer UC, Ozdemir C, Akdis M, Akdis CA. Precision/Personalized Medicine in Allergic Diseases and Asthma. Arch Immunol Ther Exp (Warsz). 2018;66(6):431-442. doi: 10.1007/s00005-018-0526-6.
26. Amarasekera M. Immunoglobulin E in health and disease. Asia Pac Allergy. 2011;1(1):12-15. doi: 10.5415/apallergy.2011.1.1.12.
27. Alvaro-Lozano M, Akdis CA, Akdis M, et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020;31 Suppl 25(Suppl 25):1-101. doi: 10.1111/pai.13189.
28. Breiteneder H, Peng YQ, Agache I, et al. Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma. Allergy. 2020;75(12):3039-3068. doi: 10.1111/all.14582.
29. Mennella C, Maniscalco U, De Pietro G, Esposito M. Ethical and regulatory challenges of AI technologies in healthcare: A narrative review. Heliyon. 2024;10(4):e26297. doi: 10.1016/j.heliyon.2024.e26297.
30. Stefanicka-Wojtas D, Kurpas D. Personalised Medicine-Implementation to the Healthcare System in Europe (Focus Group Discussions). J Pers Med. 2023;13(3):380. doi: 10.3390/jpm13030380.

31. National Academies (US) Committee on Measuring Economic and Other Returns on Federal Research Investments. Measuring the Impacts of Federal Investments in Research: A Workshop Summary. Washington (DC): National Academies Press (US); 2011. Appendix d, the impact of publicly funded biomedical and health research: a review. Available from: https://www.ncbi.nlm.nih.gov/books/NBK83123/
32. US: Department of Corporate Communications. Joint Commission. Quality and safety, sentinel events statistics released for 2020.; 2021.
33. Jakka S, Rossbach M. An economic perspective on personalized medicine. HUGO J. 2013;7(1):1-6. doi:10.1186/1877-6566-7-1.
34. Jiang F, Jiang Y, Zhi H, et al. Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol. 2017;2(4):230-243. doi: 10.1136/svn-2017-000101.
35. Serrano LP, Maita KC, Avila FR, et al. Benefits and Challenges of Remote Patient Monitoring as Perceived by Health Care Practitioners: A Systematic Review. Perm J. 2023;27(4):100-111. doi: 10.7812/TPP/23.022.
36. Kellogg KM, Hettinger Z, Shah M, et al. Our current approach to root cause analysis: is it contributing to our failure to improve patient safety? BMJ Qual Saf. 2017 May;26(5):381-387. doi: 10.1136/bmjqs-2016-005991.
37. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. N Engl J Med. 2010;363(22):2124-34. doi: 10.1056/NEJMsa1004404.
38. Ho D, Quake SR, McCabe ERB, et al. Enabling Technologies for Personalized and Precision Medicine. Trends Biotechnol. 2020;38(5):497-518. doi: 10.1016/j.tibtech.2019.12.021.
39. Lockwood W. Prevention of Medical Errors and Medication Errors Report. 2021. Available at: https://www.rn.org/courses/coursematerial-135.pdf. Accessed 2021.
40. Rodziewicz TL, Houseman B, Vaqar S, et al. Medical Error Reduction and Prevention. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
41. Wampler Muskardin TL, Paredes JL, Appenzeller S, Niewold TB. Lessons from precision medicine in rheumatology. Mult Scler. 2020;26(5):533-539. doi: 10.1177/1352458519884249.
42. Malandrino N, Smith RJ. Personalized medicine in diabetes. Clin Chem. 2011;57(2):231-40. doi: 10.1373/clinchem.2010.156901.
43. Sharma R. Mapping of global, regional and national incidence, mortality and mortality-to-incidence ratio of lung cancer in 2020 and 2050. Int J Clin Oncol. 2022;27(4):665-675. doi: 10.1007/s10147-021-02108-2.
44. Mathur S, Sutton J. Personalized medicine could transform healthcare. Biomed Rep. 2017;7(1):3-5. doi: 10.3892/br.2017.922.
45. Liao J, Li X, Gan Y, Han S, Rong P, Wang W, Li W, Zhou L. Artificial intelligence assists precision medicine in cancer treatment. Front Oncol. 2023;12:998222. doi: 10.3389/fonc.2022.998222
46. Brown JC, Gerhardt TE, Kwon E. Risk Factors for Coronary Artery Disease. [Updated 2023 Jan 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
47. Sims TJ, Boye KS, Robinson S, Kennedy-Martin T. Treatment-Related Attributes of Diabetes Therapies and How People with Type 2 Diabetes Report Their Impact on Indicators of Medication-Taking Behaviors. Patient Prefer Adherence. 2022;16:1919-1939. doi: 10.2147/PPA.S367046.
48. Esplin ED, Oei L, Snyder MP. Personalized sequencing and the future of medicine: discovery, diagnosis and defeat of disease. Pharmacogenomics. 2014;15(14):1771-1790. doi: 10.2217/pgs.14.117.
49. Mathur S, Sutton J. Personalized medicine could transform healthcare. Biomed Rep. 2017;7(1):3-5. doi: 10.3892/br.2017.922.
50. Brennan F, Lohman D, Gwyther L. Access to Pain Management as a Human Right. Am J Public Health. 2019;109(1):61-65. doi: 10.2105/AJPH.2018.304743.
51. Mosley SA, Hicks JK, Portman DG, et al. Design and rational for the precision medicine guided treatment for cancer pain pragmatic clinical trial. Contemp Clin Trials. 2018;68:7-13. doi: 10.1016/j.cct.2018.03.001.
52. McGhee SA. How the practice of allergy shows the promise and challenge of personalized medicine. Mol Genet Metab. 2011;104(1-2):3-6. doi: 10.1016/j.ymgme.2011.07.017.
53. Meiliana A, Dewi NM, Wijaya A. Personalized medicine: the future of health care. Indones Biomed J. 2016;8(3):127-146. doi: 10.18585/inabj.v8i3.271.
54. Patel CJ, Sivadas A, Tabassum R, Preeprem T, Zhao J, Arafat D, Chen R, Morgan AA, Martin GS, Brigham KL, Butte AJ, Gibson G. Whole genome sequencing in support of wellness and health maintenance. Genome Med. 2013;5(6):58. doi: 10.1186/gm462.
55. Redekop WK, Mladsi D. The faces of personalized medicine: a framework for understanding its meaning and scope. Value Health. 2013;16(6 Suppl):S4-9. doi: 10.1016/j.jval.2013.06.005.
56. Soydemir D, Seren Intepeler S, Mert H. Barriers to Medical Error Reporting for Physicians and Nurses. West J Nurs Res. 2017;39(10):1348-1363. doi: 10.1177/0193945916671934.
57. van Weel C, Kidd MR. Why strengthening primary health care is essential to achieving universal health coverage. CMAJ. 2018;190(15):E463-E466. doi: 10.1503/cmaj.170784.
58. Dayıoğlu N. Assessing the Health-economic Crisis: The Case of Turkey. Lectio Socialis. 2022;6(2):67-80. doi: 10.47478/lectio.1079624

The European Research Journal 2024;10(6):634-643 Review

DOI: https://doi.org/10.18621/eurj.1468149 *Obstetrics and Gynecology*

Exploring the role of serum sestrin 2 in patients with endometrial polyps and uterine leiomyomas: implications for early diagnosis and pathophysiology

Selim Akkaya, Teymur Bornaun, Hamid Zafer Güven

Department of Obstetrics and Gynecology, University Health Sciences Turkey, İstanbul Bağclar Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Endometrial polyps and uterine leiomyomas are common gynecological conditions that significantly affect women's health. Recent studies have begun to explore potential biomarkers that could assist in the early diagnosis and understanding of the pathophysiology of these conditions. One such biomarker is Serum Sestrin 2 (SESN2), a protein involved in cellular stress response. This review aims to synthesize research findings on the relationship between serum SESN2 levels and the presence of endometrial polyps and uterine leiomyomas. It examines the potential of SESN2 as a diagnostic tool and its role in the underlying mechanisms of these conditions. Studies suggest that SESN2 levels are elevated in patients with these conditions compared to controls, indicating its involvement in their pathophysiology. Furthermore, the review discusses the implications of these findings for clinical practice, particularly in terms of early detection and targeted therapies. Future research directions and the need for large-scale studies to validate SESN2 as a clinical marker are also addressed. This review highlights the importance of biomarkers like SESN2 in enhancing our understanding and management of gynecological disorders.

Keywords: Sestrin 2, endometrial polyp, uterine leiomyoma, biomarkers

Endometrial polyps are localized hyperplastic growths of the endometrial glands and stroma around a vascular core that originate from the surface of the endometrium [1]. These polyps are predominantly benign but can occasionally possess atypical or malignant characteristics. They are a common cause of abnormal uterine bleeding, which is observed in up to 68% of affected patients and represents the most frequent symptom associated with endometrial polyps [2].

Uterine leiomyomas, or fibroids, are benign tumors derived from the smooth muscle cells of the myometrium and are the most common pelvic tumors in women [3]. These tumors vary widely in size, number, and location within the uterus, influencing their clinical manifestations, which most frequently include excessive menstrual bleeding and pelvic discomfort [4].

The pathophysiology of both endometrial polyps and uterine leiomyomas is not fully understood, though oxidative stress and inflammatory processes

Corresponding author: Selim Akkaya, MD.,
Phone: +90 212 440 40 00, E-mail: drakkaya.selim@gmail.com

How to cite this article: Akkaya S, Bornaun T, Güven HZ. Exploring the role of serum sestrin 2 in patients with endometrial polyps and uterine leiomyomas: implications for early diagnosis and pathophysiology. Eur Res J. 2024;10(6):634-643. doi: 10.18621/eurj.1468149

Received: April 14, 2024
Accepted: June 25, 2024
Published Online: July 15, 2024

are thought to play significant roles in their development [5]. Oxidative stress, defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses, is a common pathway implicated in many pathologies, including the formation of fibroids and possibly polyps [6].

Sestrin 2 (SESN2) emerges as a critical protein in regulating oxidative stress and has been linked to various cellular responses to damage and stress [7]. It is induced under conditions of oxidative stress and plays a significant role in cell survival and metabolic regulation [8]. Elevated levels of SESN2 have been observed in patients with endometrial polyps and uterine leiomyomas, suggesting its involvement in the pathogenesis of these conditions and its potential utility as a biomarker for early diagnosis [9].

Given the prevalence and impact of endometrial polyps and uterine leiomyomas on women's health, understanding the role of biomarkers such as SESN2 could significantly enhance diagnostic accuracy and lead to more targeted therapies, ultimately improving patient outcomes. This review aims to compile and analyze the existing literature on SESN2 in relation to these common gynecological disorders and to evaluate its potential as a diagnostic and therapeutic marker [10].

ENDOMETRIAL POLYPS AND UTERINE LEIOMYOMAS

Endometrial polyps and uterine leiomyomas are two prevalent non-cancerous growths affecting the female reproductive system, with significant implications for women's health globally. Endometrial polyps are localized hyperplastic growths consisting of endometrial glands, stroma, and blood vessels that project from the lining of the uterus [11]. They vary in size, can be sessile or pedunculated, and although usually benign, they can exhibit atypical features or undergo malignant transformation in rare cases [12].

Uterine leiomyomas, commonly known as fibroids, are benign smooth muscle tumors originating from the myometrium, the muscular layer of the uterus [3]. These tumors are the most common pelvic tumors in women and can vary greatly in size, number, and location within the uterus, affecting their clinical presentation and management [13, 14]. Fibroids are recognized for their impact on menstruation, fertility, and overall quality of life, contributing to significant healthcare costs due to their high prevalence and the morbidity associated with severe cases [15].

Both conditions are important due to their high prevalence and frequently lead to diagnostic challenges and diverse treatment modalities. Understanding these conditions has evolved significantly, with current research focusing on their hormonal regulation, genetic predispositions, and potential environmental triggers [16]. Endometrial polyps and uterine leiomyomas often present similarly but have distinct pathophysiological pathways, which are crucial for tailoring individualized treatment strategies.

The relevance of these conditions in gynecological health stems from their common occurrence and the considerable impact they can have on a woman's reproductive capabilities and quality of life. Understanding and managing these conditions efficiently is critical, not only to alleviate symptoms but also to prevent potential complications such as infertility and recurrent pregnancy loss, which are significant concerns associated with these gynecological anomalies [17].

EPIDEMIOLOGY AND RISK FACTORS

The epidemiology of endometrial polyps and uterine leiomyomas highlights their significant prevalence in the female population, underscoring a major public health concern. Endometrial polyps are estimated to affect approximately 10% to 25% of women, with their prevalence increasing with age. These polyps are more commonly diagnosed in women in their 40s and 50s, particularly during the perimenopausal period, suggesting a link with hormonal changes associated with the menopausal transition [18].

Uterine leiomyomas are even more prevalent, affecting up to 70-80% of women by the age of 50 [19]. While many cases are asymptomatic and may not require intervention, a significant proportion of affected women experience symptoms severe enough to necessitate medical or surgical treatment. The onset of fibroids is rarely seen before the onset of menstruation, and their growth is often influenced by reproductive hormones, which explains their common development

during the reproductive years and often a decrease in size and symptomatology after menopause [20].

Hormonal Imbalances

Both endometrial polyps and uterine leiomyomas are influenced by hormonal imbalances, particularly by estrogens and progesterone. Estrogens promote the growth of both polyps and fibroids, while progesterone may have a complex role, potentially supporting growth in some cases while inhibiting it in others [21]. This hormonal influence is pivotal and represents a target for therapeutic intervention, such as the use of hormone modulators including selective estrogen receptor modulators (SERMs) and gonadotropin-releasing hormone (GnRH) analogs, which have been shown to reduce the size and symptoms of fibroids [22].

Genetic Predispositions

There is a significant genetic component to the risk of developing both endometrial polyps and uterine leiomyomas. The familial clustering of fibroids suggests a hereditary component, with studies identifying specific genetic alterations associated with their growth, such as mutations in the MED12 gene and other components related to the extracellular matrix and cellular proliferation [23]. Similarly, genetic predispositions have been noted in the development of endometrial polyps, with a particular association with syndromes that include a predisposition to polyp formation, such as Lynch syndrome [24].

Environmental Influences

Environmental factors also play a crucial role in the epidemiology of these conditions. Lifestyle factors such as obesity, high blood pressure, and a diet high in red meat have been linked to an increased risk of fibroids, while physical activity and a diet rich in fruits and vegetables appear to reduce this risk [25]. Exposure to environmental toxins such as phthalates and other endocrine-disrupting chemicals has also been suggested to contribute to the development of both polyps and fibroids, although more research is needed to establish these links definitively [26]. In conclusion, endometrial polyps and uterine leiomyomas are common gynecological conditions with complex multifactorial etiologies involving hormonal, genetic, and environmental components. Understanding these factors is crucial for developing prevention strategies, refining diagnostic processes, and tailoring individualized treatments that can effectively manage or mitigate the conditions.

PATHOPHYSIOLOGY AND GENETIC INSIGHTS

The pathophysiological processes underlying the formation and growth of endometrial polyps and uterine leiomyomas are complex and involve a confluence of hormonal influences, genetic mutations, and possibly, lifestyle factors. These mechanisms are not only crucial for understanding the development of these conditions but also for advancing targeted treatment strategies.

Hormonal Pathways

Both endometrial polyps and uterine leiomyomas are significantly influenced by hormonal pathways, particularly those involving estrogen and progesterone, two key regulators of the reproductive system. Estrogen promotes the proliferation of the endometrial lining and is thought to contribute to the hyperplastic growth seen in polyps [27]. In leiomyomas, estrogen acts to stimulate fibroid growth through the activation of estrogen receptors, which increases the expression of genes involved in cell proliferation and decreases those involved in apoptosis [28]. Progesterone, although traditionally considered antiproliferative, can have a complex role in the growth dynamics of these conditions. In fibroids, progesterone has been shown to contribute to fibroid growth by stimulating the production of growth factors and extracellular matrix components that provide structural support to the tumors [29].

Genetic Mutations

On a genetic level, multiple mutations have been implicated in the pathogenesis of uterine leiomyomas. For instance, mutations in the MED12 gene are among the most common genetic alterations in leiomyomas, found in up to 70% of cases [30]. These mutations may alter the function of the mediator complex, which plays a critical role in transcriptional regulation, potentially leading to dysregulated cell growth. For endometrial polyps, the genetic landscape is less well

defined, but abnormalities in genes related to hormonal regulation and inflammatory pathways are suspected [31]. Additionally, genetic predisposition plays a role, as evidenced by the higher prevalence of these conditions in certain familial and hereditary contexts, such as those associated with hereditary nonpolyposis colorectal cancer (Lynch syndrome).

Lifestyle Factors

Lifestyle factors also influence the pathophysiology of these gynecological conditions. Obesity, high-fat diet, and lack of physical activity have been associated with an increased risk of developing fibroids. These factors may influence hormone levels, particularly increasing estrogen levels, which in turn may exacerbate the growth of leiomyomas and potentially endometrial polyps [32]. Moreover, oxidative stress and inflammation, which can be exacerbated by lifestyle factors such as smoking and poor diet, have also been suggested to contribute to the pathogenesis of these conditions. Oxidative stress, in particular, can damage DNA and disrupt normal cell functions, leading to abnormal cell growth and the development of polyps and fibroids [33].

Environmental Contributions

Environmental exposures, including certain chemicals and pollutants, have been implicated in the increased risk of developing polyps and fibroids. Endocrine-disrupting chemicals, such as bisphenol A (BPA) and certain phthalates, which are prevalent in many consumer products, can mimic or interfere with the body's natural hormones, particularly estrogen, potentially contributing to the pathophysiology of these conditions [34]. In conclusion, the formation and growth of endometrial polyps and uterine leiomyomas are influenced by a complex interplay of hormonal imbalances, genetic predispositions, and environmental and lifestyle factors. Understanding these underlying mechanisms not only helps in diagnosing and managing these conditions but also opens up possibilities for preventive strategies and novel therapeutic approaches based on molecular and genetic targets.

CLINICAL PRESENTATION AND DIAGNOSIS

Endometrial polyps and uterine leiomyomas, though often asymptomatic, can present with a range of symptoms that significantly affect patients' quality of life and reproductive health. The approach to diagnosis combines clinical assessment with sophisticated imaging techniques, providing a comprehensive understanding of these conditions.

Symptoms of Endometrial Polyps and Uterine Leiomyomas

The most common symptom associated with endometrial polyps is abnormal uterine bleeding (AUB), which can manifest as irregular menstrual cycles, menorrhagia (heavy menstrual bleeding), or bleeding between periods [35]. Such symptoms can lead to anemia and significantly impact daily life, causing fatigue and other health complications. Endometrial polyps are also associated with infertility, as they can interfere with the implantation of the embryo [36].

Uterine leiomyomas may present with a similar profile of menstrual irregularities but are particularly known for causing heavy and prolonged periods. Other symptoms include pelvic pain or pressure, frequent urination, pain during intercourse, and, in some cases, complications during pregnancy such as increased risk of miscarriage or preterm labor [37]. The size and location of fibroids determine the severity and type of symptoms, with larger fibroids and those located within the uterine cavity causing more severe symptoms.

Diagnostic Procedures

The diagnosis of endometrial polyps typically involves transvaginal ultrasound (TVUS) as a first-line imaging technique. TVUS is highly effective in identifying the presence of polyps as focal hyperechoic lesions within the endometrial cavity. For a more detailed assessment, saline infusion sonohysterography (SIS) may be used, which provides a clearer image of the uterine cavity and can distinguish polyps from other intrauterine abnormalities like submucosal fibroids [38].

Uterine leiomyomas are also initially evaluated with TVUS, which can detect the tumors as well-defined, hypoechoic masses within the myometrium. The number, size, and exact location of fibroids can be assessed, which is critical for determining the appropriate management strategy. In cases where more detailed imaging is required, Magnetic Resonance Im-

aging (MRI) may be utilized. MRI offers excellent soft tissue contrast and can differentiate fibroids from other pelvic pathologies, making it invaluable particularly when surgical intervention is being considered [39].

Additionally, hysteroscopy is an essential diagnostic tool for both conditions when surgical management is planned or when the intracavitary extent of polyps or fibroids needs to be precisely determined. This procedure involves the insertion of a small camera through the cervix into the uterine cavity, providing a direct visual assessment of the endometrium, which is useful for confirming the diagnosis and during the removal of polyps or submucosal fibroids [40].

Accurate diagnosis and effective management of endometrial polyps and uterine leiomyomas rely heavily on the detailed understanding of their clinical presentations and the judicious use of advanced diagnostic tools. The symptoms, while sometimes nonspecific, are significant indicators of these conditions and can profoundly impact a woman's reproductive health and quality of life. By integrating clinical findings with advanced imaging techniques, clinicians can tailor treatment plans that address both the symptoms and the underlying causes of these prevalent gynecological conditions.

TREATMENT STRATEGIES AND MANAGEMENT

The management of endometrial polyps and uterine leiomyomas involves a spectrum of treatment options tailored to the patient's symptoms, reproductive goals, and the specifics of the condition. Treatment choices range from conservative observation to pharmacological interventions and invasive surgical procedures. The decision-making process is guided by the severity of symptoms, the patient's desire for fertility preservation, and the location and size of the lesions.

Pharmacological Interventions

For patients experiencing mild symptoms or when fertility preservation is a priority, pharmacological treatment may be the first line of approach. In the case of uterine leiomyomas, hormone-modulating therapies are commonly used to reduce symptoms and decrease fibroid size. These include:

Gonadotropin-Releasing Hormone (GnRH) Agonists

These drugs effectively shrink fibroids by creating a temporary menopausal state and decreasing estrogen levels. However, their use is typically limited to short-term preoperative periods due to the risk of significant bone density loss with long-term use [42].

Progestins and Progesterone Receptor Modulators (PRMs)

Medications like mifepristone and ulipristal acetate can control bleeding and decrease fibroid size. They act by antagonizing progesterone, which is known to promote fibroid growth [43].

Oral Contraceptives and Levonorgestrel-Releasing Intrauterine Devices (IUDs)

These are more commonly used for managing bleeding symptoms rather than reducing fibroid size. They provide effective contraception and menstrual cycle regulation, which can be beneficial in managing AUB associated with fibroids [44].

For endometrial polyps, hormonal therapy may also be used, particularly in patients who are asymptomatic or have minor symptoms. However, the effectiveness of hormonal treatments in reducing polyp size or preventing recurrence is less clear and less commonly recommended compared to their use in leiomyomas.

Surgical Procedures

When pharmacological management is ineffective or when the polyps or fibroids cause significant symptoms, surgical intervention may be necessary:

Hysteroscopic Polypectomy

This is the treatment of choice for symptomatic endometrial polyps. It involves the removal of polyps using a hysteroscope, which allows direct visualization and excision with minimal invasion [45].

Myomectomy

This surgical procedure involves the removal of fibroids while preserving the uterus, making it suitable for women who wish to maintain fertility. Myomectomy can be performed using hysteroscopic, laparoscopic, or open surgical techniques depending on the size and location of the fibroids [46].

Hysterectomy

This is the definitive treatment for fibroids and involves the removal of the uterus. It is typically reserved for women with severe symptoms who do not wish to preserve fertility, or when other treatments have failed [47].

Criteria for Choosing Treatment Paths

The choice of treatment is influenced by several factors:

Symptom Severity

More severe symptoms often require more aggressive treatment such as surgery.

Patient's Age and Desire For Children

Fertility-preserving treatments are prioritized for younger women desiring future pregnancies.

Size and Location of the Growths

Larger or unfavorably located fibroids may require surgical intervention, whereas smaller and fewer fibroids or polyps might be managed with medication.

Patient Preference and Overall Health

Consideration of the patient's personal preferences and general health condition is crucial in deciding the treatment approach.

The management of endometrial polyps and uterine leiomyomas requires a personalized approach that considers the patient's clinical presentation, lifestyle factors, and reproductive plans. With advancements in medical treatments and surgical techniques, most women can achieve significant relief from symptoms and improvement in quality of life. Ongoing research continues to refine these treatment options and may offer more targeted therapies in the future.

ROLE OF SESTRIN 2 IN PATHOGENESIS

Sestrin 2, a highly conserved protein involved in cellular stress responses, has emerged as a significant player in the pathophysiology of various human diseases, including endometrial polyps and uterine leiomyomas. Its functions span from antioxidation to modulation of metabolism and inflammation, which are pivotal in the context of these gynecological conditions.

Cellular Stress Responses

SESN2 is known for its role in protecting cells against oxidative stress and DNA damage. It acts by activating the AMP-activated protein kinase (AMPK) and regulating the mammalian target of rapamycin (mTOR) pathways, which are critical in cellular survival and metabolism [48]. In the uterine environment, oxidative stress is a recognized factor contributing to the pathogenesis of both polyps and fibroids. SESN2's activation in response to increased oxidative stress helps maintain cellular integrity by inhibiting mTOR signaling, thus potentially preventing the uncontrolled cell proliferation characteristic of polyps and leiomyomas [49].

Inflammation

The role of inflammation in the development of endometrial polyps and uterine leiomyomas is well documented, with pro-inflammatory cytokines found elevated in affected tissues. SESN2 modulates inflammatory responses by influencing NF-κB signaling pathways. By controlling these pathways, SESN2 could reduce chronic inflammation and its downstream effects, which contribute to the fibrotic processes seen particularly in leiomyomas [50].

Oxidative Stress

Oxidative stress results from an imbalance between free radicals and antioxidants in the body, leading to cell damage. SESN2 enhances the expression of various antioxidant proteins and enzymes, thus protecting cells from oxidative damage. This protective role is crucial in the endometrium, where oxidative stress can lead to mutations and cellular dysregulation, fostering the growth of polyps and fibroids [51]. Furthermore, studies have shown that SESN2 expression is upregulated in the tissues of patients with leiomyomas, suggesting that it may be a compensatory response to increased oxidative stress in these tumors [52].

Interactions with Other Cellular Mechanisms

SESN2 also interacts with other cellular pathways involved in cell survival and apoptosis, which are dys-

regulated in the pathogenesis of uterine fibroids and polyps. For example, its regulation of the p53 pathway can influence cell cycle arrest and apoptosis, processes that are often inhibited in fibroid cells and polyp cells [53]. Additionally, its role in autophagy through the AMPK and mTOR pathways can affect cellular cleanup and turnover, impacting the stability and viability of cells in the uterine lining.

IMPLICATIONS FOR TREATMENT AND RESEARCH

Understanding the role of SESN2 in the pathogenesis of endometrial polyps and uterine leiomyomas offers potential therapeutic avenues. Targeting the SESN2 pathways could lead to the development of drugs that modulate its activity, aiming to reduce oxidative stress, inflammation, and cell proliferation associated with these conditions. Moreover, SESN2 could serve as a biomarker for the early detection of these gynecological disorders, potentially guiding treatment decisions and monitoring responses to therapy [54].

SESN2 plays a multifaceted role in the pathogenesis of endometrial polyps and uterine leiomyomas through its involvement in oxidative stress response, inflammation, and cellular metabolism. Further research into SESN2 and its pathways could illuminate new strategies for managing these prevalent conditions, improving outcomes for affected women.

IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

The exploration of sestrin 2 (SESN2) as a biomarker and therapeutic target in the context of endometrial polyps and uterine leiomyomas is opening new avenues in both research and clinical management of these conditions. The potential applications and benefits of SESN2-focused research are vast, offering prospects for early diagnosis, personalized treatment strategies, and improved patient outcomes.

SESN2 as a Biomarker for Early Diagnosis

The ability of SESN2 to respond to cellular stress and inflammation, key factors in the pathogenesis of endometrial polyps and uterine leiomyomas, makes it a promising candidate for a biomarker. Early detection of these conditions remains a challenge but is crucial for effective management, especially in preserving fertility and minimizing invasive treatments. Elevated levels of SESN2 could potentially indicate the early onset of disease processes before significant symptoms manifest, allowing for earlier intervention and monitoring [56]. Future studies could focus on validating the sensitivity and specificity of SESN2 levels in blood or tissue samples as a diagnostic tool in clinical settings.

Therapeutic Interventions Targeting SESN2

Research into SESN2's role in modulating oxidative stress and inflammation suggests that it could be a target for therapeutic intervention. Developing drugs that can modulate the activity of SESN2 might help in managing the growth and symptoms of polyps and leiomyomas. For instance, enhancing the antioxidant capabilities of SESN2 or its ability to inhibit cell proliferation pathways could directly impact the development and progression of these uterine conditions [57]. Clinical trials could be designed to test such interventions, providing data on their efficacy and safety.

Integration into Personalized Medicine

The heterogeneity in the presentation and progression of endometrial polyps and uterine leiomyomas makes personalized treatment approaches necessary. Understanding individual differences in SESN2 expression and function could help tailor treatments based on a patient's genetic and molecular profile. This approach could optimize treatment efficacy and minimize side effects, particularly in managing conditions that affect diverse populations [58].

Future Research Directions

Continued research into SESN2 will also need to address several critical questions:

Mechanistic Understanding

How exactly does SESN2 interact with other cellular pathways involved in the pathogenesis of endometrial polyps and uterine leiomyomas? Answering this could uncover additional therapeutic targets.

Longitudinal Studies

What are the long-term implications of modulat-

ing SESN2 in patients with these conditions? Longitudinal studies could help understand the potential risks or benefits.

Clinical Trials

How effective are SESN2-targeted therapies in clinical practice? Rigorous clinical trials are needed to determine the practical benefits and any potential side effects of new treatments based on SESN2 modulation.

The ongoing research into sestrin 2 holds significant promise for revolutionizing the diagnosis and treatment of endometrial polyps and uterine leiomyomas. By integrating emerging data on SESN2 into clinical practice, the medical community can potentially improve diagnostic accuracy and treatment outcomes for patients suffering from these prevalent gynecological conditions. As research progresses, it is hoped that SESN2 can be fully utilized not only as a biomarker for early detection but also as a cornerstone for targeted therapeutic strategies.

CONCLUSION

The exploration of sestrin 2 in the context of endometrial polyps and uterine leiomyomas marks a significant advance in our understanding of these common yet complex gynecological disorders. As we have reviewed, the roles of sestrin 2 are multifaceted, encompassing the regulation of oxidative stress, inflammation, and cellular metabolism—key elements that contribute to the pathogenesis of these conditions.

The potential of sestrin 2 as a biomarker for early diagnosis and a target for therapeutic intervention opens new pathways for the effective management of endometrial polyps and leiomyomas. Its ability to respond to cellular stress and to modulate important metabolic and inflammatory pathways positions it as a unique marker that could help in the early detection of these conditions, potentially guiding treatment choices and monitoring therapeutic responses. This is particularly crucial given the often asymptomatic nature of these conditions in their early stages and the severe impact they can have on a woman's quality of life and reproductive health.

Furthermore, the possibility of targeting sestrin 2 in therapeutic interventions offers a promising outlook for treatments that are more precise and less invasive. By potentially inhibiting the pathways involved in the proliferation and survival of the cells that contribute to these disorders, new treatments could limit the growth of polyps and fibroids or even prevent their formation. This approach not only aims to alleviate the symptoms associated with these conditions but also addresses the underlying causes, potentially reducing the need for surgical interventions which carry inherent risks and complications.

However, while the therapeutic implications of sestrin 2 are promising, significant work remains to be done. Comprehensive clinical trials are needed to validate the efficacy and safety of these new approaches. Moreover, the integration of sestrin 2 into clinical practice will require a collaborative effort among researchers, clinicians, and patients to fully realize its potential benefits.

In conclusion, the ongoing research into sestrin 2 represents a frontier in gynecological research with the potential to significantly impact how endometrial polyps and uterine leiomyomas are diagnosed and treated. It encourages a shift towards more personalized and precise medical interventions that could greatly enhance patient outcomes. As this field evolves, it is expected that sestrin 2 will not only improve our biological understanding of these conditions but also lead to innovations in their management, heralding a new era of targeted therapy that could redefine standards of care in gynecology.

Authors' Contribution

Study Conception: SA; Study Design: SA, TB; Supervision: TB, HZG; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SA; Statistical Analysis and/or Data Interpretation: TB, HZG; Literature Review: SA; Manuscript Preparation: SA and Critical Review: SA, TB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Nijkang NP, Anderson L, Markham R, Manconi F. Endometrial polyps: Pathogenesis, sequelae and treatment. SAGE Open Med. 2019;7. doi: 10.1177/2050312119848247.
2. Salim S, Won H, Nesbitt-Hawes E, Campbell N, Abbott J. Diagnosis and management of endometrial polyps: A critical review of the literature. J Minim Invasive Gynecol. 2011;18(5):569-581. doi: 10.1016/j.jmig.2011.05.018.
3. Shokeir TA, Shalan HM, El-Shafei MM. Significance of endometrial polyps detected hysteroscopically in eumenorrheic infertile women. J Obstet Gynaecol Res. 2004;30(2):84-89. doi: 10.1111/j.1447-0756.2003.00163.x.
4. Indraccolo U, Di Iorio R, Matteo M, Corona G, Greco P, Indraccolo SR. The pathogenesis of endometrial polyps: a systematic semi-quantitative review. Eur J Gynaecol Oncol. 2013;34(1):5-22. doi: 10.12892/ejgo340101.
5. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003;188(1):100-107. doi: 10.1067/mob.2003.99.
6. Protic O, Toti P, Islam MS, et al. Possible involvement of inflammatory/reparative processes in the development of uterine fibroids. Cell Tissue Res. 2016;364(2):415-427. doi: 10.1007/s00441-015-2324-3.
7. Santulli P, Borghese B, Lemaréchal H, et al. Increased serum oxidative stress markers in women with uterine leiomyoma. PLoS One. 2013;8(8):e72069. doi: 10.1371/journal.pone.0072069.
8. Özcan O, Erdal H, Çakırca G, Yönden Z. [Oxidative stress and its impacts on intracellular lipids, proteins and DNA]. J Clin Exp Invest. 2015;6(3):331-336. doi: 10.5799/ahinjs.01.2015.03.0545. [Article in Turkish]
9. Maeda H, Akaike T. Nitric oxide and oxygen radicals in infection, inflammation, and cancer. Biochemistry (Mosc). 1998;63(7):854-865. doi: 10.1007/978-1-4615-5081-5_18.
10. Toyokuni S, Okamoto K, Yodoi J, Hiai H. Persistent oxidative stress in cancer. FEBS Lett. 1995;358(1):1-3. doi: 10.1016/0014-5793(94)01368-B.
11. Pejic S, Kasapovic J, Todorovic A, Stojiljkovic V, Pajovic SB. Lipid peroxidation and antioxidant status in blood of patients with uterine myoma, endometrial polypus, hyperplastic and malignant endometrium. Biol Res. 2006;39(4):619-629. doi: 10.4067/S0716-97602006000500005.
12. Gong L, Wang Z, Wang Z, Zhang Z. Sestrin2 as a potential target for regulating metabolic-related diseases. Front Endocrinol (Lausanne). 2021;12:751020. doi: 10.3389/fendo.2021.751020.
13. Yang JH, Kim KM, Kim MG, et al. Role of sestrin2 in the regulation of proinflammatory signaling in macrophages. Free Radic Biol Med. 2015;78:156-167. doi: 10.1016/j.freeradbiomed.2014.11.002.
14. Yi L, Li F, Yong Y, et al. Upregulation of sestrin-2 expression protects against endothelial toxicity of angiotensin II. Cell Biol Toxicol. 2014;30(3):147-156. doi: 10.1007/s10565-014-9276-3.
15. Shin J, Bae J, Park S, et al. mTOR-Dependent Role of Sestrin2 in Regulating Tumor Progression of Human Endometrial Cancer. Cancers (Basel). 2020;12(9):2515. doi: 10.3390/cancers12092515.
16. Lu C, Jiang Y, Xu W, Bao X. Sestrin2: multifaceted functions, molecular basis, and its implications in liver diseases. Cell Death Dis. 2023;14(2):160. doi: 10.1038/s41419-023-05669-4.
17. Xu L, Liu Z, Wang H, et al. SESN2 Could Be a Potential Marker for Diagnosis and Prognosis in Glioma. Genes (Basel). 2023;14(3):701. doi: 10.3390/genes14030701.
18. Ala M. Sestrin2 in cancer: a foe or a friend? Biomark Res. 2022;10(1):29. doi: 10.1186/s40364-022-00380-6.
19. Kim KR, Peng R, Ro JY, Robboy SJ. A diagnostically useful histopathologic feature of endometrial polyp: the long axis of endometrial glands arranged parallel to surface epithelium. Am J Surg Pathol. 2004;28(8):1057-1062. doi: 10.1097/01.pas.0000128659.73944.f3.
20. Salim S, Won H, Nesbitt-Hawes E, Campbell N, Abbott J. Diagnosis and management of endometrial polyps: a critical review of the literature. J Minim Invasive Gynecol. 2011;18(5):569-581. doi: 10.1016/j.jmig.2011.05.018.
21. Hamani Y, Eldar I, Sela HY, Voss E, Haimov-Kochman R. The clinical significance of small endometrial polyps. Eur J Obstet Gynecol Reprod Biol. 2013;170(2):497-500. doi: 10.1016/j.ejogrb.2013.07.011.
22. Peterson WF, Novak ER. Endometrial polyps. Obstet Gynecol. 1956;8(1):40-49.
23. Jovanovic AS, Boynton KA, Mutter GL. Uteri of women with endometrial carcinoma contain a histopathological spectrum of monoclonal putative precancers, some with microsatellite instability. Cancer Res. 1996;56(8):1917-1921.
24. Pal L, Niklaus AL, Kim M, Pollack S, Santoro N. Heterogeneity in endometrial expression of aromatase in polyp-bearing uteri. Hum Reprod. 2008;23(1):80-84. doi: 1093/humrep/dem346.
25. Maia H, Pimentel K, Silva TMC, et al. Aromatase and cyclooxygenase-2 expression in endometrial polyps during the menstrual cycle. Gynecol Endocrinol. 2006;22(4):219-224. doi: 10.1080/09513590600585955.
26. Nogueira AA, Sant'Ana de Almeida EC, Poli Neto OB, Zambelli Ramalho LN, Rosa e Silva JC, Candido dos Reis FJ. Immunohistochemical expression of p63 in endometrial polyps: evidence that a basal cell immunophenotype is maintained. Menopause. 2006;13(5):826-830. doi: 10.1097/01.gme.0000242274.32278.a2.
27. Dal Cin P, Vanni R, Marras S, et al. Four cytogenetic subgroups can be identified in endometrial polyps. Cancer Res. 1995;55(7):1565-1568. doi: 10.1016/0165-4608(96)85299-X.
28. Tanos V, Berry KE, Seikkula J, et al. The management of polyps in female reproductive organs. Int J Surg. 2017;43:7-16. doi: 10.1016/j.ijsu.2017.05.012.
29. McLennan CE, Rydell AH. Extent of endometrial shedding during normal menstruation. Obstet Gynecol. 1965;26(5):605-621.
30. Altaner S, Gucer F, Tokatli F, et al. Expression of Bcl-2 and Ki-67 in Tamoxifen-Associated Endometrial Polyps: Comparison with Postmenopausal Polyps. Oncol Res Treat. 2006;29(8-9):376-380. doi: 10.1159/000094443.
31. Banas T, Pitynski K, Mikos M, Cielecka-Kuszyk J, Cielecka D. Endometrial Polyps and Benign Endometrial Hyperplasia Have Increased Prevalence of DNA Fragmentation Factors 40 and 45 (DFF40 and DFF45) Together With the Antiapoptotic B-

Cell Lymphoma (Bcl-2) Protein Compared With Normal Human Endometria. Int J Gynecol Pathol. 2018;37(5):431-440. doi: 10.1097/PGP.0000000000000442.
32. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol. 2009;33(1):102-108. doi: 10.1002/uog.6259.
33. Annan JJ, Aquilina J, Ball E. The management of endometrial polyps in the 21st century. Obstetr Gynaecol. 2012;14(1):33-38. doi: 10.1111/j.1744-4667.2011.00091.x.
34. Vitale SG, Haimovich S, Laganà AS, et al. Endometrial polyps. An evidence-based diagnosis and management guide. Eur J Obstet Gynecol Reprod Biol. 2021;260:70-77. doi: 10.1016/j.ejogrb.2021.03.017.
35. Sasaki LMP, Andrade KRC, Figueiredo ACMG, Wanderley M da S, Pereira MG. Factors Associated with Malignancy in Hysteroscopically Resected Endometrial Polyps: A Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2018;25(5):777-785. doi: 10.1016/j.jmig.2018.02.004.
36. Runowicz CD, Costantino JP, Wickerham DL, et al. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). Am J Obstet Gynecol. 2011;205(6):535.e1-535.e5. doi: 10.1016/j.ajog.2011.06.067.
37. Lee JH, Budanov AV, Park EJ, et al. Sestrin as a feedback inhibitor of TOR that prevents age-related pathologies. Science. 2010;327(5970):1223-1228. doi: 10.1126/science.1182228.
38. Ro SH, Fay J, Cyuzuzo CI, et al. SESTRINs: Emerging Dynamic Stress-Sensors in Metabolic and Environmental Health. Front Cell Dev Biol. 2020;8:603421. doi: 10.3389/fcell.2020.603421.
39. Ryu D, Jo YS, Lo Sasso G, et al. A metabolic role for mitochondria in palmitate-induced cardiac myocyte apoptosis. Diabetologia. 2010;53(11):2435-2445. doi: 10.1152/ajpheart.2000.279.5.H2124.
40. Hu X, Xu Q, Wan H, et al. Sestrin2 protects against acute myocardial infarction by enhancing autophagy and reducing oxidative stress. Redox Biol. 2020;32:101504. doi: 10.1016/j.jphs.2020.11.012.
41. Zhong Z, Sanchez-Lopez E, Karin M. More than an antioxidant: the role of sestrin2 in regulating metabolism and preventing disease. J Hepatol. 2020;72(1):173-181. doi: 10.3390/ijms21134714.
42. Choi AMK, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med. 2013;368(15):1845-1846. doi: 10.1056/NEJMra1205406.
43. Park HW, Park H, Ro SH, et al. Hepatic expression of detoxifying enzymes is decreased in human subjects with nonalcoholic fatty liver disease and in mice with diet-induced steatosis. J Hepatol. 2012;57(2):780-787. doi: 10.1016/j.jphs.2020.11.012.
44. Li X, Guo J, Jiang X, et al. Involvement of sestrin2 in the regulation of endoplasmic reticulum stress in diabetes. Diabetes Res Clin Pract. 2019;156:107834. doi: 10.18632/oncotarget.7601.
45. Sun Y, Chen X, Zhang X, Shen X, Wang M, Wang X. Protective effects of sestrin2 in cardiovascular diseases: Promising therapeutic potential. Rev Cardiovasc Med. 2021;22(1):275-285. doi: 10.1016/j.heliyon.2024.e27110.
46. Zhang J, Li Y, Jiang S, Yu H, An W. Role of sestrin2 in the regulation of proinflammatory signaling in macrophages. Free Radic Biol Med. 2015;78:156-167. doi: 10.1016/j.freeradbiomed.2014.11.002.
47. Suh JH, Kim K, Choi JH, Paik SR, Kim H. Sestrin2 is crucial for the survival of human pancreatic beta cells under oxidative stress. Diabetes Metab Res Rev. 2018;34(2). doi: 10.1016/j.mad.2020.111379.
48. Liang Y, Zhu J, Huang H, et al. SESN2/sestrin 2 induction-mediated autophagy and inhibitory effect of isorhapontigenin (ISO) on human bladder cancers. Autophagy. 2016;12(8):1229-1239. doi: 10.1080/15548627.2016.1179403.
49. Chen KB, Xuan Y, Shi WJ, Chi F, Xing R, Zeng YC. Sestrin2 expression is a favorable prognostic factor in patients with non-small cell lung cancer. Am J Transl Res. 2016;8(4):1903-1909.
50. Zhao B, Shah P, Budanov AV, et al. Sestrin2 protein positively regulates AKT enzyme signaling and survival in human squamous cell carcinoma and melanoma cells. J Biol Chem. 2014;289(52):35806-35814. doi: 10.1074/jbc.M114.595397.
51. Chae HS, Gil M, Saha SK, et al. Sestrin2 expression has regulatory properties and prognostic value in lung cancer. J Pers Med. 2020;10(3):109. doi: 10.3390/jpm10030109.
52. Byun JK, Choi YK, Kim JH, et al. A positive feedback loop between Sestrin2 and mTORC2 is required for the survival of glutamine-depleted lung cancer cells. Cell Rep. 2017;20(3):586-599. doi: 10.1016/j.celrep.2017.06.066.
53. Torkzaban M, Machado P, Gupta I, Hai Y, Forsberg F. Contrast-enhanced ultrasound for monitoring non-surgical treatments of uterine fibroids: A systematic review. Ultrasound Med Biol. 2021;47(1):3-18. doi: 10.1016/j.ultrasmedbio.2020.09.016.
54. Stoelinga B, Juffermans L, Dooper A, et al. Contrast-enhanced ultrasound imaging of uterine disorders: A systematic review. Ultrason Imaging. 2021;43(5):239-252. doi: 10.1177/01617346211017462.
55. Sandberg EM, Tummers FHMP, Cohen SL, van den Haak L, Dekkers OM, Jansen FW. Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids: a systematic review and meta-analysis. Fertil Steril. 2018;109(4):698-707.e1. doi: 10.1016/j.fertnstert.2017.11.033.
56. Laughlin-Tommaso SK, Lu D, Thomas L, et al. Short-term quality of life after myomectomy for uterine fibroids from the COMPARE-UF Fibroid Registry. Am J Obstet Gynecol. 2020;222(4):345.e1-345.e22. doi: 10.1016/j.ajog.2019.09.052.
57. Marret H, Fritel X, Ouldamer L, et al. Therapeutic management of uterine fibroid tumors: updated French guidelines. Eur J Obstet Gynecol Reprod Biol. 2012;165(2):156-164. doi: 10.1016/j.ejogrb.2012.07.030.
58. Yao X, Stewart EA, Laughlin-Tommaso SK, Heien HC, Borah BJ. Medical therapies for heavy menstrual bleeding in women with uterine fibroids: a retrospective analysis of a large commercially insured population in the USA. BJOG. 2017;124(2):322-330. doi: 10.1111/1471-0528.14383.

The European Research Journal 2024;10(6):644-651 Case Report

DOI: https://doi.org/10.18621/eurj.1465494 *Pediatric Nephrology*

An earthquake reality: Fasciotomy wounds and treatments

Hakan Erdoğan[1], Arzu Oto[2], Gamze Yerci[3], Gülcan Koçer[4], Burcu Menekşe[4], Berna Aktürk[4], Ümit Yıldırım[4], Şefika Bozdemir[5]

[1]Department of Pediatric Nephrology, University of Health Sciences, Bursa Faculty of Medicine, Bursa, Türkiye, [2]Department of Pediatric Intensive Care Unit, University of Health Sciences, Bursa Faculty of Medicine, Bursa, Türkiye, [3]Department of Underwater and Hyperbaric Medicine, University of Health Sciences, Bursa Faculty of Medicine, Bursa, Türkiye, [4]Department of Pediatrics, University of Health Sciences, Bursa Faculty of Medicine, Bursa, Türkiye, [5]Department of Pediatric Infection Diseases, University of Health Sciences, Bursa Faculty of Medicine, Bursa, Türkiye

ABSTRACT

Earthquake-induced crush syndrome and subsequent acute kidney injury are important issues that affect morbidity and mortality. Fasciotomies prolong the length of stay in intensive care unit in patients with compartment syndrome due to the complications it causes. Infections and delayed wound healing are two common complications among these. Therefore, early closure of fasciotomy wounds is recommended. Although different treatments can be applied for treatment of wounds, data on this subject in pediatric patients are insufficient. We report the case of a 15-year-old girl who developed acute renal failure due to crush syndrome after being trapped in the wreckage for 9 hours and undergoing fasciotomy procedures for four locations, in the left extremity, two in the thigh and two in the cruris. Hemodialysis, antihypertensive, and antibiotic treatment were administered during the intensive care follow-up due to acute kidney injury, hypertension, and sepsis. With negative pressure therapy, silver alginate wound dressing, and hyperbaric oxygen therapy, all wounds epithelialized within two months. However, rehabilitation for drop foot syndrome caused by nerve cuts in the left extremity continues.

Keywords: Earthquake, fasciotomy wounds, negative pressure therapy (VAC), hyperbaric oxygen therapy

In compartment syndrome, fasciotomy is the only known treatment option, it can usually save the extremities [1]. In surgical fasciotomy, the release of the skin and muscle fascia results in a sudden decrease in compartment pressure and a significant increase in the volume of the affected muscle compartment [2]. However, reperfusion injury caused by fasciotomy and complications from the procedure has both local and systemic consequences [3]. Although it is recommended for the fasciotomy wounds to be closed as soon as possible to reduce the risk of complications, doing so may result in increased muscle pressure and re-compartment syndrome [4]. Prolonged hospitalization, wound infection, the need for advanced surgery for skin grafting, osteomyelitis, pain, nerve injury, permanent muscle weakness, chronic venous insufficiency, and cosmetic issues are all important issues for fasciotomy patients [5]. Wound management aims to debride necrotic tissues and minimize damage by preventing moisture loss. For this

Corresponding author: Hakan Erdoğan, MD., Prof.,
Phone: +90 224 975 00 00, E-mail: drerdoganha@yahoo.com

How to cite this article: Erdogan H, Oto A, Yerci G, Kocer G, Menekse B. Akturk B, Yıldırım U, Bozdemir S. An earthquake reality: Fasciotomy wounds and treatments. Eur Res J. 2024;10(6):644-651. doi: 10.18621/eurj.1465494

Received: April 15, 2024
Accepted: June 26, 2024
Published Online: July 16, 2024

purpose, there are different treatment options for wound healing. These include skin grafts, negative pressure therapy (Vacuum Assisted Closure-VAC), dermal apposition techniques (Gradual Suture Approximation), and hyperbaric oxygen therapy (HBOT). It is unclear which technique is best for treating wounds, especially in children [6]. Here, a 15-year-old girl was trapped under the wreckage after the earthquake and had two fasciotomies in the cruris and thigh due to compartment syndrome in the left lower extremity, who also had crush syndrome, is presented.

CASE PRESENTATION

After 9 hours under the wreckage, a 15-year-old girl developed compartment syndrome in her left lower extremity. It was discovered that she had four fasciotomies on her left thigh and cruris, and four sessions of hemodialysis (HD) treatment following acute kidney damage (AKI) due to compartment syndrome. At the family's request, the case was referred and admitted to the Bursa City Hospital Pediatric Intensive Care Clinic (PICU) eight days later. The patient's physical examination revealed a moderately poor general condition, GCS 15, and a suture secondary to trauma in the frontal region, she was followed up in the room air at admission. There were fasciotomies on both medial and lateral sides of the left cruris and thigh, distal pulses were palpable and no fractures were detected in the extremities. The patient had no problems in left hip and knee movements, her left foot flexion and dorsiflexion were limited and she had a drop foot. She had intense fragrant discharge in more than one of the thigh fasciotomies. Fasciotomies in the thigh area had a cavitary appearance. The laboratory values in the follow-up are shown in Table 1. Cranial CT and MRI scans were reported as normal. On admission, the patient had a urine output of <0.3 ml/kg/hour. For forced diuresis, 3000 ml/m^2 IV fluids and 2 mg/kg/day furosemide were started. Piperacillin-Tazobactam and Teicoplanin were started ampirically according to the glomerular filtration rate (GFR) after cultures were taken from the wound sites. Intermittent HD was restarted in the case whose urine output was not sufficient despite IV fluid and furosemide, and blood pressure systolic-diastolic >95p. On the 17th day, HD was performed due to fluid overload symptoms, blood pressures above 99p, and consciousness change. Repeated cranial diffusion MRI and CT scan findings were evaluated as normal. Antihypertensive treatment with amlodipine, enalapril and propranolol was started for the case with high blood pressure values. Since the blood pressure was sometimes above 99p during this period, IV esmolol treatment was also applied for 2 days in addition to this

Table 1. Case laboratory findings

	Day 1	Day 3	Day 7	Day 14	Day 21	Day 30	Day 40	Day 60
Hb (g/dL)	9.4	8.1	8.2	7.2	7	8.6	9.4	11.3
Hct (%)	26.9	23.6	24	20.4	20.2	26.8	27.9	33.4
WBC (10^3/mm^3)	20.3	28.7	19.3	13.4	14.3	17.3	9.2	7.4
Plt (10^3 /mm^3)	142	134	143	163	163	315	319	329
Urea (mg/dL)	91.4	106.1	138.7	175.9	107.2	20.1	22.3	19.3
Creatinin (mg/dL)	3.48	4.05	3.65	4.02	1.5	0.44	0.38	0.42
CK (IU/L)	9526	2664	441	217	60	57	61	60
Na (mEq/L)	128	128	130	131	152	144	136	136
K (mEq/L)	3.6	3.5	5.1	5.3	2.6	4.8	4.5	4.2
Ca (mg/dl)	8.6	8.7	7.5	9.3	12.3	8.6	9.8	9.8
Albumin (g/L)	26.6	21.8	25.4	20.5	30.3	30.4	39	38.9
CRP (mg/L)	46.1	15.3	90.5	28	25.5	47.1	25.1	4.2
Procalcitonin	5.83	2.86	67.8	2.38	0.57	0.85	0.47	0.19

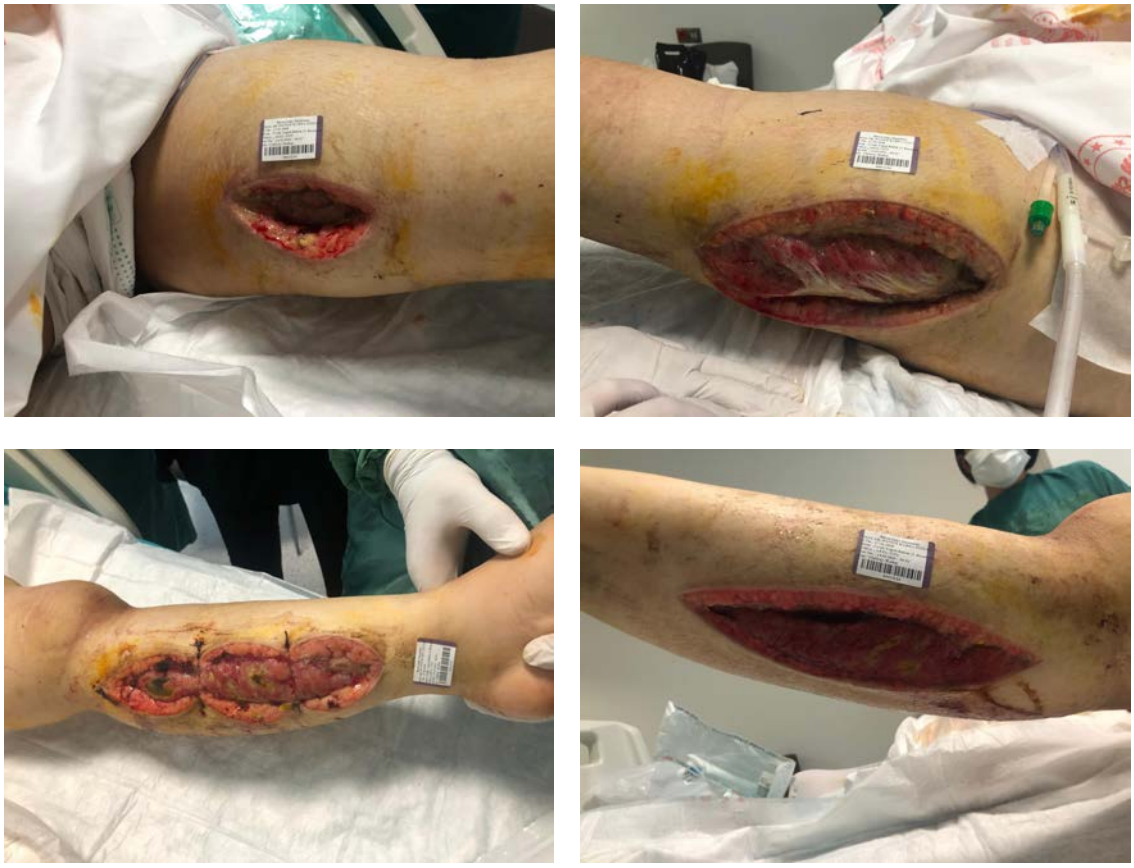


Fig 1. **Fasciotomy wounds at admission.**

treatment. HD was performed 8 times in the first 17 days of the patient's stay in the intensive care unit and 23 days in the ward. The patient was followed up for 37 days in the intensive care unit and 23 days in the ward. In the following days, urination increased, the findings of compartment syndrome completely regressed, and she did not need HD again. After the 30th day of her hospitalization, her antihypertensive treatments were gradually reduced and she was discharged with amlodipine 0.3 mg/kg.

All four fasciotomy wounds were followed closely from the first day of admission (Fig. 1). Infections due to fasciotomy wounds are shown in Table 2. The antibiotic treatment was changed to meropenem and colistin based on GFR due to the reproduction of Acinetobacter Baumannii in the initial wound cultures. Since the growth of colistin-sensitive Acinetobacter Baumannii continued in repetitive wound cultures, it was continued for 30 days. Vancomycin was added to the treatment on the 20th day of hospitalization due to Staphylococcus Hominis growth in the blood culture, and when there was no growth in the blood cultures, it was discontinued on the 14th day of treatment. Physiotherapy was applied for pain-related limitation of motion and subsequent muscle weakness. The patient who was experiencing mood disorders from the beginning did not comply with physiotherapy and avoided mobilization, prophylactic low molecular weight heparin was administered during her stay. The child was evaluated by a psychiatric physician and mirtazepine treatment was started.

In addition to antibiotic treatments for fasciotomy wounds, VAC therapy, silver alginate wound dressing and HBOT were applied along with general wound care from hospitalization. The patient had sutures on the 3rd thigh wound at the earthquake center on admission due to the "Gradual Suture Approximation" procedure (Fig. 1). During this period, the wound looked infected and the sutures were removed, considering that this procedure was conducted early. A total of 8 sessions of VAC therapy were applied to the medial and lateral thigh fasciotomies, changing every three

Table 2. Case wound culture results

	Wound 1	Wound 2	Wound 3	Wound 4
Day 1	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)
Day 14	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)
Day 21	No Reproduction	No Reproduction	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)
Day 25	Epitelized	Epitelized	*A. Baumannii* (Colistin sensitive)	*A. Baumannii* (Colistin sensitive)
Day 30			No Reproduction	No Reproduction
Day 46			No Reproduction	No Reproduction
Day 60			Epitelized	

days due to their cavitary appearance. The VAC instillation system, which provided periodic irrigation with the hypochlorous acid solution (Crystalin®: pH7.1, active chloride content 200 ppm), was used in the last three VAC applications due to the reproduction in the wound culture. No cavities were observed in the two distal fasciotomies, so daily dressing with silver alginate wound dressing was applied. HBOT treatment, which was planned to be done daily, could only be applied for a total of 12 sessions due to the patient's lack of compliance.

Bleeding in the form of leakage was common, es-

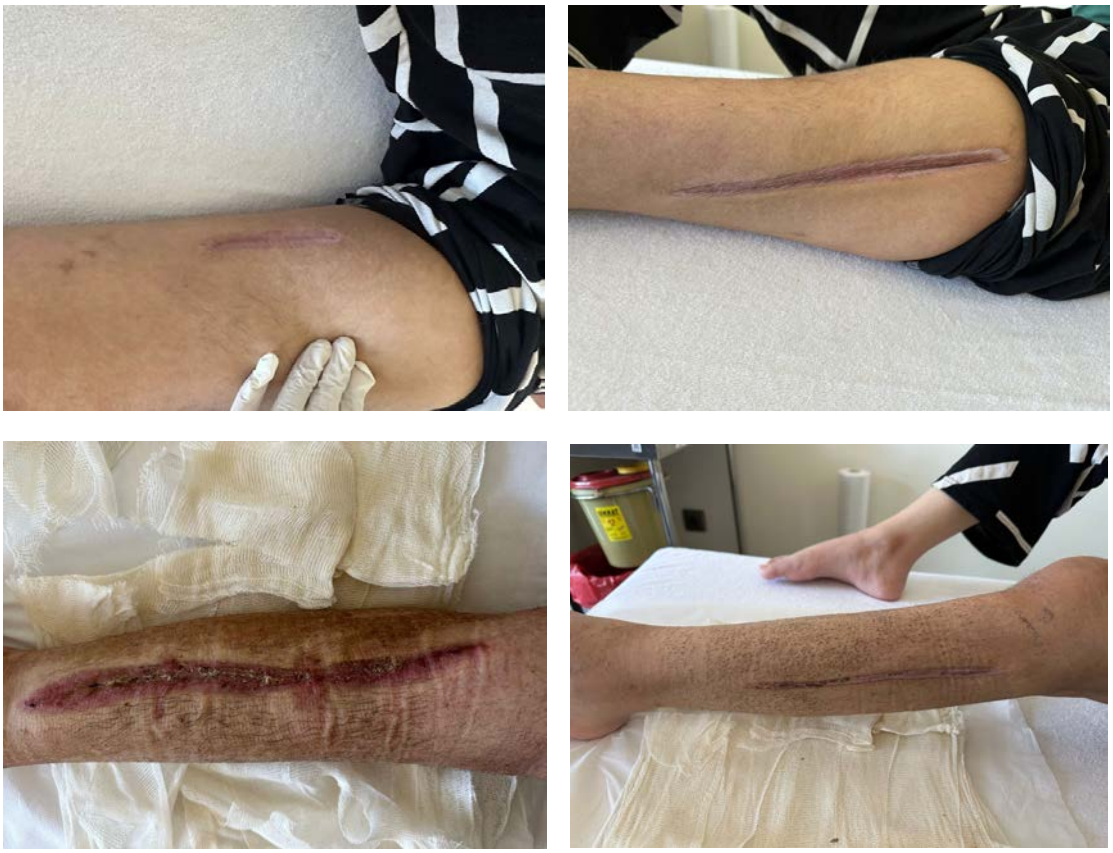


Fig 2. Fasciotmy wounds 3 months after admission.

pecially during VAC treatment. Erythrocyte transfusion was performed 4 times in the first 15 days. Hemodialysis treatment, frequent blood draw for examination purposes and bleeding due to VAC treatment were considered causes of anemia. With these treatments, there was no bacterial growth in the first and second fasciotomy wounds on the thigh on the 21st day and the wounds were epithelized on the 28th day. No bacterial growth was found in the third and fourth wounds of the cruris on the 30th day, these wounds epithelized on the 60th day after discharge. It took the longest time for the number 3 wound, located medial to the cruris, to be fully epithelialized. The images of the patient's fasciotomy wounds in the 3rd month are shown in Fig. 2. The patient, whose physiotherapy compliance is still not good, has lost muscle mass in both legs as well as drop foot syndrome in the left leg where a fasciotomy was performed. EMG was planned for evaluation of nerve damage but the patient did not consent to EMG. Kidney functions and blood pressures returned to normal, and outpatient controls in child psychiatry and pediatric nephrology are performed.

DISCUSSION

According to official figures, 50,783 people died and 122 thousand people were injured in the earthquakes of 7.8 and 7.5 Mw, which occurred 9 hours apart, the epicenter of which was in Kahramanmaraş Pazarcık and Ekinözü districts on February 6, 2023. Compartment syndrome and subsequent AKI are common problems associated with mortality in cases dug out of the wreckage during earthquakes [7]. However, wound infection and sepsis are other serious problems in patients who develop compartment syndrome and therefore undergo fasciotomy [8]. The damage caused by these wounds lengthens the hospital stay, even if infection problems are well managed. The healing process is hampered by psychological trauma caused by the disaster, particularly in pediatric patients. During our patient's hospitalization, serious complications such as compartment syndrome, AKI, the need for dialysis as a result of this, stage 2 hypertension, psychological problems that required treatment, wound infection, and sepsis developed. All these complications are closely related. Data on the care and treatment of fasciotomy wounds following compartment syndrome are inadequate in the literature, particularly in pediatric patients. Therefore, in particular, fasciotomy wounds, related infections and their treatment are primarily discussed here.

Compartment Syndrome is a medical emergency characterized by decreased blood flow and oxygen delivery to muscle and nerve tissue as well as increased intramuscular pressure. Increased compartment pressure can result in muscle necrosis, nerve damage, and limb loss. In order to reduce intramuscular pressure, a fasciotomy is performed to surgically release the fascia surrounding the compartment. It is critical to close the fasciotomy wounds as soon as possible to minimize infection, functional loss, and cosmetic risks.

Data on compartment syndrome and fasciotomy in major earthquakes are limited, and unfortunately, the majority of them are from Türkiye. One of the biggest data sources we have is the data obtained from 639 patients in 15 hospitals due to crush syndrome in the 1999 Marmara earthquake by Erek *et al*. In this article, it was reported that fasciotomies were opened in 323 (50.5%) of the patients and that these fasciotomy wounds were associated with sepsis and mortality [7]. However, information about the treatment and prognosis of the wounds is not given here. Reproduction in the fasciotomy wounds and sepsis were the factors that most affected the patient's morbidity in our case. Aerobic and opportunistic anaerobic bacteria have been reported to be the most commonly isolated microorganisms in the wound area of crush syndrome patients [9]. The importance of early closure of fasciotomy wounds was mentioned again in the study evaluating the infections in crush syndrome after the Marmara earthquake, and especially the risk of bleeding and infection was emphasized. In this study, 51 growths in 41 fasciotomy wounds from 30 patients were evaluated, and the three most common bacteria in wound cultures were found to be Acinetobacter spp (23 reproduction), Pseudomonas aeruginosa (11 reproduction), and Methicillin Resistance Staphylococcus aureus (9 reproduction) [8]. Acinetobacter Baumannii growth was observed in recurrent cultures taken from four wound sites in our patient, and colistin and meropenem treatment was administered in accordance with the antibiogram.

After the Marmara earthquake, 16 patients who underwent fasciotomy were sent to a plastic surgery

center 400 km away from the earthquake center, and the treatment results of these patients were reported by Duman *et al*. [10]. Accordingly, in 4 patients (25%) had their extremity amputated after fasciotomy, 4 patients (25%) required rehabilitation after treatment, and 8 patients (50%) were reported to have fully recovered. Again, it was stated in this study that only one patient had two fasciotomy wounds that required rehabilitation after treatment, but no information was provided about the wound treatment. No case has been reported in the literature with 4 fasciotomy wounds on the same extremity after an earthquake. Although there were 4 fasciotomy wounds in the same extremity, all wounds healed and closed, and no amputation was required in our case, however, unfortunately, drop foot syndrome developed due to nerve damage in this extremity, and the patient's rehabilitation continues.

A partial-thickness skin graft is a popular option for the early closure of fasciotomy wounds. However, the wound area should be suitable for this and there should be no infection. The use of grafts is limited by problems such as sensory loss during follow-up, the risk of graft non-adherence, and, in some cases, poor cosmetic appearance [6]. This treatment option was excluded for our patient due to early wound infections and a large wound area. Another accepted treatment option for fasciotomy wounds is Gradual Suture Approximation. Staples are placed along the wound edges, and the suture is passed crosswise through these staples and tied lightly. Every 48 hours, it is tightened at the bedside. It is a simple, safe and cheap method. Staple displacement, ischemia, and tissue necrosis are among the rare complications. The presence of infection in the wound area, however, limits this treatment option [6]. Our patient also had stitches in accordance with the "Gradual Suture Approximation" procedure carried out at the earthquake center. Considering that these sutures would not be effective on the infected wound, they were removed. Since the wound closure was good in later periods, this procedure was not needed.

In our case, VAC therapy and a silver alginate wound dressing technique were used to treat four large fasciotomy wounds on the left extremity. VAC therapy is a treatment that involves sterile closure of the wound area and continuously or intermittently applying negative pressure to the wound. It promotes wound healing by increasing local blood flow, decreasing local edema, promoting granulation tissue development, fighting infection by reducing bacterial colonization, providing a moist wound environment, and accelerating epithelialization. Antiedema efficacy of VAC therapy gains importance in tissue healing in wounds with prominent edema, such as fasciotomy wounds [6, 11]. The use of VAC in the treatment of fasciotomy wounds in pediatric patients has been shown to be safe and effective. In their 2009 article, Gabriel *et al*. reported that the closure time of fasciotomy wounds with the use of VAC therapy in pediatric patients was 5 to 10 days and no complications were encountered. [12]. However, there are also negative opinions about VAC treatment. In a recent study, Kakagia *et al*. [4] discovered a higher need for skin grafts, a higher cost, and a more extended treatment duration in the treatment of VAC when compared to the Stepped Stitching Approach technique.

In general, VAC therapy is well tolerated in pediatric patients. The most common side effects are pain, bleeding and skin irritation, but they are usually rare. It is critical to monitor bleeding in fasciotomy wounds after VAC application [11, 13]. Our patient's resistance to treatment was caused by the presence of pain. Furthermore, there was oozing bleeding in wound 3 at first, but no such complication was observed in the other wounds. We believe that VAC treatment was the most effective treatment for our patient's wounds. Grafts were not required in our patients, although they were mentioned in the literature, particularly after VAC treatment. Considering our patient's wounds, wound healing times were deemed reasonable.

Silver alginate wound dressings are preferred in the treatment of fasciotomy wounds with abundant exudate due to their natural absorbent and antimicrobial properties [14]. In our patient, silver alginate absorbent wound dressing was preferred for distal fasciotomy wounds with a more limited cavitary structure. It was regarded as an adjunctive treatment to the primary treatment: VAC treatment.

HBOT is a treatment based on breathing 100% oxygen in a pressurized cabin. It is intended to benefit from the antiedema and antihypoxic effects of increased tissue partial oxygen pressure with HBOT in crush wounds. The literature on the use of HBOT in pediatric fasciotomy wounds is limited, but available

data suggest that these patients may benefit from HBOT. In a 1998 article, it was reported that the results obtained with HBOT in 13 children with crush injury were at a desirable level when evaluated on the parameters of mortality, soft tissue loss and amputation rate [15]. In a case series of 3 cases in which HBOT and VAC treatment were applied together and supported with a gradual suturing approach, it was reported that the wounds closed in 3-18 days [16]. The 12 sessions of HBOT treatment used on our patient significantly aided the other two treatments. However, in one case that emerged from the wreckage, taking the patient with a mask to a closed area was deemed the most significant disadvantage of this treatment in pediatric patients. We had to discontinue this treatment on some days when she received HBOT due to the patient's resistance. With VAC, silver alginate wound dressings, and HBOT, the wounds on the thigh healed in one month and the wounds on the cruris closed in two months in our patient.

CONCLUSION

As a result, Türkiye is located within the earthquake zone; unfortunately, new earthquakes are expected. In these earthquakes, fasciotomy wounds will also be encountered along with many problems. One of the primary goals should be to perform surgical fasciotomies only when necessary. Although this intervention is often life-saving, it sometimes causes serious complications. All treatment options for these wounds should be considered, and appropriate treatment should be planned. Silver alginate wound dressings and HBOT, both VAC therapy and supportive treatments, appear to be good options for pediatric patients. However, we need more data on this subject especially for the children.

Informed Consent

Written informed consent was obtained from the patient's family for the publication of this case report.

Authors' Contribution

Study Conception: HE, AO; Study Design: HE, AO; Supervision: HE, AO; Funding: N/A; Materials: AO, GY, BM; Data Collection and/or Processing: GK, ÜY, BA; Statistical Analysis and/or Data Interpretation: GY, AO, ŞB; Literature Review: BA, BM, GY; Manuscript Preparation: HE, AO, GY and Critical Review: GY, ŞB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Gresh M. Compartment syndrome in the pediatric patient. Pediatr Rev. 2017;38(12):560-565. doi: 10.1542/pir.2016-0114.
2. Schmidt AH. Acute compartment syndrome. Injury. 2017;48:S22-S25. doi: 10.1016/j.injury.2017.04.024.
3. Vaillancourt C, Shrier I, Vandal A, et al. Acute compartment syndrome: how long before muscle necrosis occurs? CJEM. 2004;6(3):147-154. doi: 10.1017/s1481803500006837.
4. Kakagia D, Karadimas E, Drosos G, Ververidis A, Trypsiannis G, Verettas D. Wound closure of leg fasciotomy: comparison of vacuum-assisted closure versus shoelace technique. A randomised study. Injury. 2014;45(5):890-893. doi: 10.1016/j.injury.2012.02.002.
5. Heemskerk J, Kitslaar P. Acute compartment syndrome of the lower leg: retrospective study on prevalence, technique, and outcome of fasciotomies. World J Surg. 2003;27(6):744-747. doi: 10.1007/s00268-003-6691-7.
6. Jauregui JJ, Yarmis SJ, Tsai J, Onuoha KO, Illical E, Paulino CB. Fasciotomy closure techniques: A meta-analysis. Journal Orthop Surg. 2017;25(1):2309499016684724. doi: 10.1177/2309499016684724.
7. Erek E, Sever MS, Serdengeçti K, , et al. An overview of morbidity and mortality in patients with acute renal failure due to crush syndrome: the Marmara earthquake experience. Nephrol Dial Transplant. 2002;17(1):33-40. doi: 10.1093/ndt/17.1.33.
8. Kazancioglu R, Cagatay A, Calangu S, et al. The characteristics of infections in crush syndrome. Clin Microbiol Infect. 2002;8(4):202-206. doi: 10.1046/j.1469-0691.2002.00371.x.
9. Dire DJ. Infection following wounds, bites and burns. Infectious Disease in Emergency Medicine. Philadelphia: Lippincott-Raven, 1998: pp. 231-260.
10. Duman H, Kulahci Y, Sengezer M. Fasciotomy in crush injury resulting from prolonged pressure in an earthquake in Turkey. Emerg Med J. 2003;20(3):251-252. doi: 10.1136/emj.20.3.251.
11. Baharestani M, Amjad I, Bookout K, Fleck T, Gabriel A, Kaufman, D. V.A.C. Therapy in the management of paediatric wounds: clinical review and experience. Int Wound J. 2009;6:1-26. doi: 10.1111/j.1742-481X.2009.00607.x.
12. Gabriel A, Heinrich C, Shores J, et al. Outcomes of vacuum-

assisted closure for the treatment of wounds in a paediatric population: case series of 58 patients. J Plast Reconstr Aesthet Surg. 2009;62(11):1428-1436. doi: 10.1016/j.bjps.2008.06.033.
13. Bussell HR, Aufdenblatten CA, Gruenenfelder C, Altermatt S, Tharakan SJ. Comparison of lower extremity fasciotomy wound closure techniques in children: vacuum-assisted closure device versus temporary synthetic skin replacement. Eur J Trauma Emerg Surg. 2019;45(5):809-814. doi: 10.1007/s00068-018-0985-9.
14. King A, Stellar JJ, Blevins A, Shah KN. Dressings and Products in Pediatric Wound Care. Adv Wound Care (New Rochelle). 2014;1;3(4):324-334. doi: 10.1089/wound.2013.0477.
15. Waisman D, Shupak A, Weisz G, Melamed Y. Hyperbaric oxygen therapy in the pediatric patient: the experience of the Israel Naval Medical Institute. Pediatrics. 1998;102(5):E53. doi: 10.1542/peds.102.5.e53.
16. Weiland DE. Fasciotomy closure using simultaneous vacuum-assisted closure and hyperbaric oxygen. Am Surg. 2007;73(3):261-266. doi: 10.1177/000313480707300313.