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CONTENT - СОДРЖИНА

PUBLIC HEALTH- ЈАВНО ЗДРАВЈЕ

DEFINING THE PHYSICAL ACTIVITY ENVIRONMENT IN PRIMARY SCHOOLS ACROSS NORTH MACEDONIA: COSI STUDY
Katerina Mihajlova, Lorraine Silver Wallace, Aleksandra Stamenova, Igor Spiroski
ДЕФИНИРАЊЕ НА ОКОЛИНАТА ЗА ФИЗИЧКА АКТИВНОСТ ВО ОСНОВНИТЕ УЧИЛИШТА ВО СЕВЕРНА МАКЕДОНИЈА – COSI СТУДИЈА
Катерина Михајлова, Лорејн Силвер Волис, Александра Стаменова, Игор Спироски 5

LESSONS FROM A MEDICAL STUDENT-RUN PUBLIC HEALTH JOURNAL CLUB- SURVEY STUDY
Karla Kroflin, Karla Lužaić, Kristina Krstanović, Bruno Korac, Sanja Musić-Milanović
ЛЕКЦИИ ОД КЛУБ ЗА НАУЧНИ ТРУДОВИ ВО ЈАВНО ЗДРАВСТВО ВОДЕН ОД СТУДЕНТИ ПО МЕДИЦИНА - АНКЕТНА СТУДИЈА
Карла Крофлин[1], Карла Лужаиќ, Кристина Крстановиќ, Бруно Кораќ, Сања Мусиќ-Милановиќ ... 14

ASSESSMENT OF DISEASE BURDEN CAUSED BY BIOLOGICAL AGENTS ASSOCIATED WITH UNSAFE FOOD IN THE REPUBLIC OF NORTH MACEDONIA
Aneta Kostova, Gordana Ristovska, Dance Gudeva-Nikovska
ПРОЦЕНКА НА ОПТОВАРУВАЊЕ СО БОЛЕСТИ ПРЕДИЗВИКАНИ ОД БИОЛОШКИ АГЕНСИ ПОВРЗАНИ СО НЕБЕЗБЕДНА ХРАНА ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА
Анета Костова, Гордана Ристовска, Данче Гудева-Никовска 26

OPINIONS AND ATTITUDES OF PARENTS AND HEALTHCARE WORKERS ON HEALTH EDUCATION AND IMMUNIZATION IN TUTIN MUNICIPALITY
Mithat Eminovic, Selma Habibovic
МИСЛЕЊА И СТАВОВИ НА РОДИТЕЛИ И ЗДРАВСТВЕНИ РАБОТНИЦИ ЗА ЗДРАВСТВЕНА-ТА ЕДУКАЦИЈА И ИМУНИЗАЦИЈАТА ВО ОПШТИНА ТУТИН
Митхат Еминовиќ, Селма Хабибовиќ 40

CLINICAL SCIENCE- КЛИНИЧКИ ИСТРАЖУВАЊА

MEASURING THE EFFICACY OF TREATMENT WITH NEUROFEEDBACK METHOD IN PATIENTS WITH AFFECTIVE DISORDERS
Aleksandar Risteski, Slavica Arsova, Elizabet Miceva-Velichkoska, Ana Filipce, Stefanija Mitrovska
МЕРЕЊЕ НА ЕФИКАСНОСТ НА МЕТОДАТА NEUROFEEDBACK ПРИ ТРЕТМАН НА ПАЦИЕН-ТИ СО АФЕКТИВНИ РАСТРОЈСТВА
Александар Ристески, Славица Арсова, Елизабет Мицева-Величкоска, Ана Филипче, Стефанија Митровска 51

INFLUENCE OF VANCOMYCIN AND MEROPENEM LOADING ON COMPRESSIVE STRENGTH OF POLYMETHYL METHACRYLATE BONE CEMENT
Danica Popovska, Nikola Avramov, Milan Samardziski, Ilir Shabani, Alan Andonovski, Milena Bogojevska-Doksevska, Slavcho Stojmenski
ВЛИЈАНИЕ НА ВАНКОМИЦИНОТ И МЕРОПЕНЕМОТ ВРЗ МЕХАНИЧКИТЕ КАРАКТЕРИСТИ-КИ НА ПОЛИМЕТИЛМЕТАКРИЛАТЕН КОСКЕН ЦЕМЕНТ
Даница Поповска, Никола Аврамов, Милан Самарџиски, Илир Шабани, Алан Андоновски, Милена Богојевска Доксевска, Славчо Стојменски 63

THE EFFECT OF WIDE SWADDLING ON ALPHA HIP ANGLE IN NEWBORNS AND INFANTS
Marina Komnenovikj, Zoran Bozinovski, Daniela Georgieva, Milena Bogojevska-Doksevska, Dejan Damjanovikj, Igor Atanasovski
ЕФЕКТОТ НА ШИРОКИОТ ПОВОЈ ВРЗ АЛФА АГОЛОТ КАЈ НОВОРОДЕНЧИЊА И ДОЕНЧИЊА
Марина Комненовиќ, Зоран Божиновски, Даниела Георгиева, Илир Шабани, Милена Богојевска-Доксевска, Дејан Дамјановиќ, Игор Атанасовски 73

COMPARISON OF THE EFFECTS OF HIGH-INTENSITY LASER WITH LOW-INTENSITY LASER IN PATIENTS WITH KNEE OSTEOARTHRITIS
Valentina Koevska, Erieta Nikolikj-Dimitrova, Biljana Mitrevska, Cvetanka Gjerakaroska-Savevska, Marija Gocevska, Biljana Kalcovska, Maja Manoleva, Daniela Gecevska, Ana Krstevska

СПОРЕДБА НА ЕФЕКТИТЕ ОД ЛАСЕР СО ВИСОК ИНТЕНЗИТЕТ И ЛАСЕР СО НИЗОК ИНТЕНЗИТЕТ КАЈ ПАЦИЕНТИ СО ОСТЕОАРТРИТИС НА КОЛЕНОТО
Валентина Коевска, Ериета Николиќ-Димитрова, Билјана Митревска, Цветанка Ѓеракароска -Савевска, Марија Гоцевска, Билјана Калчовска, Маја Манолева, Даниела Гечевска 83

ORAL HEALTH- ОРАЛНО ЗДРАВЈЕ

ANALYSIS OF PERIAPICAL PROCESSES AND BONE LOSS WITH 2D AND 3D RADIOLOGICAL DIAGNOSTICS
Marina Eftimoska, Mario Jurhar, Vasilka Rendzova, Emilija Stefanovska, Stevica Ristovska

АНАЛИЗА НА ПЕРИАПИКАЛНИ ПРОЦЕСИ И КОСКЕН ГУБИТОК СО 2D И 3D РАДИОЛОШКА ДИЈАГНОСТИКА
Марина Ефтимоска, Марио Јурхар, Василка Ренџова, Емилија Стефановска, Стевица Ристовска 94

TITRATABLE ACIDITY AND PH OF COMMERCIAL MOUTHWASHES: A COMPREHENSIVE ANALYSIS
Marija Andonovska, Vlatko Kokolanski, Spiro Spasovski, Bojan Poposki, Kiro Ivanovski, Julijana Nikolovska, Olga Gigopulu

ТИТРАЦИСКАТА КИСЕЛОСТ И РН НА КОМЕРЦИЈАЛНИ ВОДИЧКИ ЗА ПЛАКНЕЊЕ НА УСТА: ДЕТАЛНА АНАЛИЗА
Марија Андоновска, Влатко Коколански, Спиро Спасовски, Бојан Попоски, Ќиро Ивановски, Јулијана Николовска, Олга Гигопулу 108

CASE REPORT- ПРИКАЗ НА СЛУЧАЈ

DRUG-INDUCED VASCULITIS WITH MULTI-ORGAN INJURY IN A SPLENECTOMISED PATIENT AND MYCOPHENOLATE MOFETIL THERAPY – A CASE REPORT
Zanina Pereska, Niko Bekjarovski, Lidija Petkovska , Natasa Simonovska, Aleksandra Babulovska, Kiril Naumoski, Filip Gucev

МЕДИКАМЕТОЗНО-ИНДУЦИРАН ВАСКУЛИТИС СО МУЛТИОРГАНСКА ПОВРЕДА КАЈ СПЛЕНЕКТОМИРАН ПАЦИЕНТ И ТЕРАПИЈА СО МИКОФЕНОЛАТ МОФЕТИЛ - ПРИКАЗ НА СЛУЧАЈ
Жанина Переска, Нико Беќаровски, Лидија Петковска, Наташа Симоновска, Александра Бабуловска, Кирил Наумоски, Филип Гучев 121

AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY (APROP), TIMELY SCREENING AND APPROPRIATE TREATMENT - CASE REPORT
Igor Isjanovski, Andrea Stojanovska, Emilija Gjoshevska-Dashtevska

ЗАДНА АГРЕСИВНА ПРЕМАТУРНА РЕТИНОПАТИЈА (APROP), НАВРЕМЕН СКРИНИНГ И СООДВЕТЕН ТРЕТМАН - ПРИКАЗ НА СЛУЧАЈ
Игор Исјановски, Андреа Стојановска, Емилија Ѓошевска-Даштевска 130

PUBLIC HEALTH

DEFINING THE PHYSICAL ACTIVITY ENVIRONMENT IN PRIMARY SCHOOLS ACROSS NORTH MACEDONIA: COSI STUDY

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Key words: primary schools, children, physical activity, physical activity environment, COSI

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Abstract

Encouraging children to engage in physical activity (PA) is crucial for their overall development. The school environment can play a significant role in shaping children's PA habits, which in turn can positively impact their overall health and wellbeing. The aim of this study was to describe characteristics of the PA environment in primary schools across North Macedonia using data from the World Health Organization's European Childhood Obesity Surveillance Initiative (COSI)–6th round. Materials and Methods: A primary school representative (n=111) responded to questions regarding the PA environment, which included questions about having outdoor and indoor playgrounds and gymnasiums, using of outdoor playgrounds outside of the school hours and during unfavorable weather conditions and organizing PA in and outside of the school hours. Descriptive statistics were conducted to depict the PA environment in primary schools across North Macedonia. Results: Most primary schools had an outdoor playground (94.6%), provided ≥2 hours per week of physical education lessons (89.2%), and had an indoor gymnasium (83.8%). However, smaller primary schools (≤29 pupils) were significantly less likely to have an indoor gymnasium. Approximately half of the primary schools (48.5%) offered organized sport/physical activities ≥1 time per week outside of school hours. Outside of school hours, most primary schools permitted the use of outdoor play areas (77.1%). Conclusion: In conclusion, while the overall PA environments were positive, all Macedonian primary schools did not possess adequate recreational facilities and space for students to be engaged in regular PA. Thus, there is a pressing need for collaborative efforts among schools, local and national authorities to address this issue effectively, aiming to combat childhood obesity and promote increased PA among young students.

ЈАВНО ЗДРАВЈЕ

ДЕФИНИРАЊЕ НА ОКОЛИНАТА ЗА ФИЗИЧКА АКТИВНОСТ ВО ОСНОВНИТЕ УЧИЛИШТА ВО СЕВЕРНА МАКЕДОНИЈА – COSI СТУДИЈА

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Клучни зборови: основни училишта, деца, физичка активност, средина за физичка активност, COSI

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Печатарски права: ©2025. Катерина Михајлова, Лорејн Силвер Волис, Александра Стаменова, Игор Спироски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа оригиналниот(ите) автор(и) и изворот.

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Извадок

Охрабрувањето на децата да се вклучат во физичка активност (ФА) е од клучно значење за нивниот развој. Училишната средина може да игра значајна улога во обликувањето на навиките за ФА кај децата, што, пак, може позитивно да влијае на нивното целокупно здравје и благосостојба. Целта на оваа студија беше да се опишат карактеристиките на околината за ФА во основните училишта низ цела Северна Македонија користејќи податоци од 6-тиот круг на Иницијативата за следење на дебелината кај децата во Европа (COSI) на Светската здравствена организација. Материјали и методи: Претставник на основно училиште (n=111) одговори на прашања во врска со средината за ФА, кои вклучуваа прашања за поседување на надворешно и внатрешно игралиште и сала, користење на надворешното игралиште надвор од училишните часови и во неповолни временски услови и организирање на ФА во и надвор од училишните часови. Беше спроведена дескриптивна статистика за да се прикаже средината за ФА во основните училишта во Северна Македонија. Резултати: Повеќето основни училишта имаа надворешно игралиште (94,6%), обезбедуваа ≥2 часа неделно часови по физичко образование (89,2%) и имаа внатрешна сала (83,8%). Сепак, основните училишта со помал број на запишани ученици (≤29 ученици) имаа значително помала веројатност да имаат внатрешна сала. Приближно половина од основните училишта (48,5%) нудеа организирани спортски/физички активности ≥еднаш неделно надвор од училишните часови. Надвор од училишните часови, повеќето основни училишта дозволуваа користење на надворешните простори за игра (77,1%). Заклучок: Иако целокупните средини за ФА беа позитивни, сите македонски основни училишта не поседуваат соодветни рекреативни објекти и простор за учениците да се вклучат во редовна ФА. Оттука, постои итна потреба за заеднички напори помеѓу училиштата, локалните и националните власти за ефективно решавање на ова прашање, со цел да се борат против дебелината кај децата и да се промовира зголемена ФА меѓу младите ученици.

Introduction

Globally, physical activity (PA) is on the decline, with less than 50% of European children and adolescents meeting recommended criteria.[1] As children's participation in PA declines, risk of various chronic diseases such as obesity, hypertension, type 2 diabetes, and cancer increases.[2,3] The World Health Organization (WHO) defines PA as any bodily movement fueled by skeletal muscles requiring energy expenditure, encompassing various activities such as play, sports, transportation, recreation, and physical education.[4] Regular PA has been shown to promote children's mental health and psychological well-being,[5,6] while also being tied to improved academic performance.[7-10]

During the academic year (≈9 months annually), European children spend most of their weekdays at school, where they sit for extended periods during academic lessons. Data from longitudinal studies with objective measures of PA suggest that the standard model of a school is poorly suited for the promotion of PA as MVPA (moderate to vigorous physical activity) begins to decline and sedentary behavior begins to increase from around the time young children first enter schools.[11]

In response to rising obesity rates, North Macedonia recently amended its law to increase the amount of time children spend in physical education classes per week, but also proposed strategies to promote PA throughout each school day.[12] The potential impact of this new law in North Macedonia could be far reaching in not only increasing daily PA but also mitigating obesity risk among young children. A recent school-based physical education intervention program in Lithuania resulted in not only increased PA engagement, but also positively affected somatic anxiety, personality anxiety, and social anxiety among children aged six to nine years.[13]

Recognizing that many children do not engage in regular PA for a variety of reasons (e.g., psychological, social, environmental, and demographic factors)[4,14-16], primary schools can potentially offer an environment to promote regular PA. The aim of this study was to describe the characteristics of the PA environment in primary schools across North Macedonia using data from the 6th round of the WHO's European Childhood Obesity Surveillance Initiative (COSI).

Materials and Methods

Data utilized in this study were collected between October and December 2022 as part of the 6th round of WHO COSI in North Macedonia. Comprehensive WHO COSI methodology reports have been previously published.[17] The Ethics Committee of the Ss. Cyril and Methodius University - Faculty of Medicine in Skopje approved the North Macedonia WHO COSI-6th round protocol (approval 03-2140/1 from 06.05.2022).

A representative sample of primary schools (n=111), located within each of the ten regional Centers of Public Health, participated in the survey.

Following completion of data collection, research assistants from the Institute of Public Health of North Macedonia reviewed each school form for accuracy. Next, these data

were entered into WHO-COSI's electronic software system (Open Clinica—Open Clinica LLC, Waltham, MA, USA) and then electronically transferred to the Regional European WHO Office for quality review and verification.

Primary School Physical Activity Environment Assessment

A designated primary school representative (e.g., headmaster/headmistress, principal) completed the mandatory WHO COSI-6th round school form that included questions regarding the primary school PA environment. The following six questions used a dichotomous response format (yes or no): (1) Does your school have an outdoor playground?, (2) Does your school have an indoor gymnasium?, (3) Is it permitted to use the outdoor playground in extreme weather conditions?, (4) Is it permitted to use the outdoor playground outside of school hours?, (5) Is it permitted to use the gym outside of school hours?, and (6) Does your school organize any sport/physical activities at least once a week for primary school children outside school hours?

Two questions were combined to assess the frequency of physical education lessons, including: (1) Does your educational program include physical education? and (2) In this current school year, how much time each week does your school provide physical education lessons for the pupils of each class participating in this project? To align with national physical education guidelines in North Macedonia,[11] responses were dichotomized as either yes (≥2 hours per week physical education lessons) or no (<2 hours per week physical education lessons).

Statistical Analyses

Descriptive analyses were conducted to illustrate the prevalence of primary school PA environment indicators overall and across second grade enrollment size in North Macedonia. Second-grade enrollment, at each primary school, was used to classify schools as either small (≤29 pupils) or large (≥30 pupils). Chi-square ($\chi 2$) analyses were performed to examine differences based on primary school enrollment size. Statistical significance was set at $p<0.05$ *a priori*. The IBM® Statistical Package for the Social Sciences, ® Version 28.0.1.1(14) (SPSS+, Chicago, Illinois) was used for all statistical analyses.

Results

Table 1. Second-grade enrollment of primary schools participating in World Health Organization European Childhood Obesity Surveillance Initiative—6th Round

Second Grade Enrollment	Schools %	Pupils M±SD
Small (≤29 pupils)	47.7	20.5±5.5
Large (≥30 pupils)	Pupils M±SD	45.2±14.7

In North Macedonia, a total of 111 primary schools participated in the WHO-COSI-6th round. As shown in Table 1, slightly less than half (47.7%) of primary schools enrolled ≤29 pupils in the second grade.

The prevalence of PA environment indicators of primary schools participating in the WHO COSI-6th round are shown in Table 2. Most primary schools had an outdoor playground (94.6%), provided ≥2 hours per week of physical education lessons (89.2%), and had an indoor gymnasium (83.8%). However, smaller primary schools (≤29 pupils) were significantly less likely to have an indoor gymnasium.

Approximately half of the primary schools (48.5%) offered organized sport/physical activities ≥1 time per week outside of school hours. Outside of school hours, most primary schools permitted use of outdoor play areas (77.1%).

Table 2. Prevalence of physical activity environment indicators of primary schools

Physical Activity Environment Indicators	Overall %	Second Grade Enrollment	
		Small (≤29 pupils) %	Large (≥30 pupils) %
Indoor gymnasium (gym)	83.8	75.5	91.4
Outdoor playground (play) area(s)	94.6	96.2	93.1
≥2 hours per week of physical education lessons	89.2	86.8	91.4
School organizes sport/physical activities, ≥1 time per week, outside of school hours	48.5	52.1	45.5
Use of outdoor play areas permitted during extreme weather conditions	14.0	17.3	10.9
Use of outdoor play area(s) permitted outside of school hours	77.1	82.0	72.7
Use of indoor gym permitted outside of school hours	21.6	22.4	20.8

Bold text denotes statistically significant differences between primary school enrollment ($p<0.05$).

Discussion

This study addresses an important gap in furthering our understanding of the primary schools PA environment across North Macedonia. Findings generated in this study can be used to monitor and develop PA environment-related guidelines and interventions for primary schools in North Macedonia. Overall, the PA primary school environment in North Macedonia was found to be positive. Most schools had both an indoor gymnasium and an outdoor playground. Additionally, nine of ten primary schools provided physical education lessons ≥2 hours per week. Our findings were similar to those of Korzycka's study on Polish primary schools,[18] particularly in terms of the availability of indoor gym facilities, outdoor play areas, and organized sports classes. In Korzycka's study, larger primary schools, with an enrollment of 30 pupils or more, were more likely to have a gymnasium. The underlying reasons for this finding should be explored in greater detail in the future across North Macedonia. Additionally, analyses should be conducted to ascertain differences in children's PA levels in the

primary school PA environments.

In a recent study, Prosheva *et al.* conducted a comprehensive assessment of primary school physical environments (n=320) across North Macedonia.19 In relation to the PA environment within schools included in their sample, those in urban areas and attended by Macedonian or multiethnic students had significantly higher chances of using school premises for PAs outside of school hours compared to schools in rural areas and/or attended by Albanian students. Additionally, 47 primary schools reported no access to school premises for after-school physical activities, while 102 reported partial access. Another study focused on the importance of designing outdoor spaces to encourage physical activity and improve children's health. This study, conducted across five primary schools in Turkey, employed various methods such as behavior mapping, physical evaluations of schoolyards, and interviews with students, teachers, and administrators. The results highlighted common features of schoolyards and the types of activities students participated in. Active students who walked to school had lower BMI levels compared to sedentary ones, and students at schools with larger yards also tended to have lower BMI values. Most students favored larger, greener schoolyards.

One major challenge identified was overcrowding during recess, which limited opportunities for physical activity. Schoolyards with better landscape designs were more popular and positively influenced student satisfaction.20

A similar study in Norway focused on monitoring schoolchildren's physical activity in relation to the availability of physical activity equipment. The study found that 73% of boys and 57% of girls in primary school reported engaging in daily physical activity during recess, compared to only 38% of boys and 21% of girls in secondary school. Boys were generally more active than girls. The research indicated that secondary school students with more outdoor facilities were nearly three times more likely to engage in daily physical activity than those with fewer facilities. Specific features, such as soccer fields, playground equipment, and sledding hills, were linked to increased activity for boys, while sledding hills were a key factor for girls. No significant patterns were observed for primary school students, likely due to their naturally higher activity levels. [21] In Norway, schools offer multiple recess periods and a longer after-lunch break, contributing up to 40% of the recommended 60 minutes of daily physical activity.[22]

Previous research has demonstrated that school environment factors, such as the availability of outdoor equipment and the presence of supervision, can positively influence physical activity levels during recess. Adding more equipment and providing supervision has been shown to boost activity levels during school time. [23-27]

A study at Rochester Elementary School explored whether children were more physically active in an activity-friendly environment compared to a traditional school setting. It compared three environments: a traditional classroom, "The Neighborhood" (which encouraged more movement), and a "Standing Classroom" with standing desks. The study also tested replacing traditional desks with vertical workstations as a practical solution. Physical activity was measured using accelerometers, showing no significant differences between systems. The study found that "The Neighborhood" led to a 50% increase in

physical activity throughout the school day, as children walked or played while learning. When standing desks were introduced to a traditional classroom, physical activity levels were similar to those in the Standing Classroom, suggesting that the building design, not just educational technology, influenced the increase in activity. While limited research exists on modifying school environments for physical activity, previous studies indicate that access to activity-related equipment, like soccer balls, increases activity, especially under supervision.[28]

A study in Japan highlights the importance of addressing environmental factors to encourage physical activity during recess and shows that promoting positive perceptions of school facilities may be particularly effective for boys at lunch recess and for girls at morning recess. This study explored how the perceived school environment affected physical activity among elementary school children during recess. Boys who believed their school had good equipment for physical activity engaged in more moderate activity during lunch recess, and those who perceived good facilities participated in more vigorous activity and less sedentary behavior. Similarly, girls who thought the school had good facilities spent more time in moderate and vigorous activity during morning recess. However, girls who saw the equipment as good engaged in less light physical activity. [29]

Limitations

Although there are several limitations to our research, when comparing our findings with those of other studies, we can still observe positive results. Several factors should be considered regarding the limitations of our study. Firstly, while the WHO COSI-6th round includes a nationally representative sample of Macedonian primary schools, the cross-sectional design limits our ability to establish causality. Secondly, as with all observational studies that rely on self-reports, response bias is a potential concern. Thirdly, due to the nature of secondary analyses, we were unable to modify or expand upon the questions and responses in the WHO COSI-6th. Finally, we identified only one previously published WHO COSI study 18 that addressed similar research questions and analyses to our own.

Conclusion

In conclusion, while the overall school-related physical activity (PA) environments were positive, not all Macedonian primary schools have sufficient recreational facilities and space for students to engage in physical activities. Therefore, there is a significant need for collaborative efforts between schools and local authorities to address this issue effectively, with the goal of combating childhood obesity and promoting increased physical activity among young students.

References

1. Górna S, Pazdro-Zastawny K, Basiak-Rasała A, Krajewska J, Cichy I, Rokita A, Zatoński T. Physical activity and sedentary behaviors in Polish children and adolescents. Archives de Pédiatrie 2023; 30 (1): 42-47, ISSN 0929-693X. https://doi.org/10.1016/j.arcped.2022.11.010
2. Janssen I, LeBlanc AG. Systematic review of the health benefits of physical activity and

fitness in school-aged children and youth. Int J Behav Nutr Phys Act. 2010;7(40). https://doi.org/10.1186/479-5868-7-40

3. Poitras VJ, Gray CE, Borghese MM, Carson V, Chaput J-P, Janssen I, et al. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. Appl Physiol Nutr Metab. 2016;41(6):S197–239 doi: 10.1139/apnm-2015-0663.
4. World Health Organization 2022, accessed 9 June 2024, https://www.who.int/news-room/fact-sheets/detail/physical-activity
5. Biddle SJH, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. Brit J Sports Med. 2011;45:886–95 DOI: 10.1136/bjsports-2011-090185
6. Babic M, Morgan PJ, Plotnikoff RC, Lonsdale C, White RL, Lubans DR. Physical activity and physical self-concept in youth: systematic review and meta-analysis. Sports Med. 2014;44:1589–601 DOI: 10.1007/s40279-014-0229-z
7. Álvarez-Bueno C, Pesce C, Cavero-Redondo I, Sánchez-López M, Garrido-Miguel M, Martínez-Vizcaíno V. Academic achievement and physical activity: a meta-analysis. Pediatrics. 2017;140(6):e20171498 DOI: 10.1542/peds.2017-1498
8. Khan NA, Hillman CH. The relation of childhood physical activity and aerobic fitness to brain function and cognition: a review. Pediatr Exerc Sci. 2014;26(2):138–46 doi: 10.1123/pes.2013-0125
9. Owen KB, Parker PD, Van Zanden B, MacMillan F, Astell-Burt T, Lonsdale C. Physical activity and school engagement in youth: a systematic review and meta-analysis. Educ Psych. 2016;51(2):129–45 DOI: 10.1080/00461520.2016.1151793
10. Santana CCA, Azevedo LB, Cattuzzo MT, Hill JO, Andrade LP, Prado WL. Physical fitness and academic performance in youth: a systematic review. Scand J Med Sci Sports. 2017;27(6):579–603 DOI: 10.1111/sms.12773
11. Bailey R, Ries F, Scheuer C. Active schools in Europe—A review of empirical findings. Sustainability. 2023 Feb 20;15(4):3806. https://doi.org/10.3390/su15043806
12. World Health Organization (WHO). North Macedonia changes law to increase the amount of time for physical activity in schools. Available from: https://www.who.int/europe/news/item/24-04-2020-north-macedonia-changes-law-to-increase-the-amount-of-time-for-physical-activity-in-schools#:~:text=North%20Macedonia%20recently%20amended%20its%20law%20to%20increase,opportunities%20for%20physical%20activity%20throughout%20the%20school%20day Accessed: June 10, 2024.
13. Kliziene I, Cizauskas G, Sipaviciene S, Aleksandraviciene R, Zaicenkoviene K. Effects

of a physical education program on physical activity and emotional well-being among primary school children. Int J Environ Res Public Health. 2021;18(14):7536. DOI: 10.3390/ijerph18147536

14. Hallal PC, Bo Andersen L, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380:247–57 DOI: 10.1016/S0140-6736(12)60646-1
15. Centers for Disease Control and Prevention. Cancer prevention and control. Current physical activity guidelines. Atlanta, USA2016. Retrieved March 18, 2019 Available from: https://www.cdc.gov/cancer/dcpc/prevention/policies_practices/physical_activity/guidelines.htm
16. Welk GJ. The youth physical activity promotion model: A conceptual bridge between theory and practice. Quest. 1999;51:5–23.

doi:.1080/00336297.1999.10484297
17. Breda J, McColl K, Buoncristiano M, et al. Methodology and implementation of the WHO European Childhood Obesity Surveillance Initiative (COSI). Obesity Rev 2021; 22(S6):e13215.

doi:10.1111/obr.13215
18. Korzycka M, Jodkowska M, Oblacińska A, Fijałkowska A. Nutrition and physical activity environments in primary schools in Poland – COSI study. Ann Agric Environ Med. 2020; 27(4): 605–612. doi: 10.26444/aaem/114223
19. Prosheva S, Kjosevska E, Velikj Stefanovska V. Assessment of the physical environment situation in primary schools in the Republic of North Macedonia. Arch Pub Health [Internet]. 2020;12(3):5-15. doi.org/10.3889/aph.2020.5418
20. Ozdemir A, Yilmaz O. Assessment of outdoor school environments and physical activity in Ankara's primary schools. Journal of Environmental Psychology, 2008; 28(3):287-300. https://doi.org/10.1016/j.jenvp.2008.02.004
21. Haug E, Torsheim T, Sallis JF, Samdal O. The characteristics of the outdoor school environment associated with physical activity. Health Education Research. 2010;28(2):248-256. https://doi.org/10.1093/her/cyn050
22. Ridgers ND, Stratton G, Fairclough SJ. Physical activity levels of children during school playtime. Sports medicine. 2006;36:359-71 DOI: 10.2165/00007256-200636040-00005
23. Sallis JF, McKenzie TL, Conway TL, Elder JP, Prochaska JJ, Brown M, et al. Environmental interventions for eating and physical activity: a randomized controlled trial in middle schools. American journal of preventive medicine. 2003; 24(3):209-17. doi: 10.1016/s0749-3797(02)00646-3.
24. Verstraete SJ, Cardon GM, De Clercq DL, De Bourdeaudhuij IM. Increasing children's physical activity levels during recess periods in elementary schools: the effects of provid-

ing game equipment. The European Journal of Public Health. 2006;16(4):415-9. doi: 10.1093/eurpub/ckl008.

25. Stratton G, Mullan E. The effect of multicolor playground markings on children's physical activity level during recess. Preventive medicine. 2005;41(5-6):828-33. DOI: 10.1016/j.ypmed.2005.07.009

26. Ridgers ND, Stratton G, Fairclough SJ, Twisk JW. Long-term effects of a playground markings and physical structures on children's recess physical activity levels. Preventive medicine. 2007;44(5):393-7. DOI: 10.1016/j.ypmed.2007.01.009

27. Barnett TA, O'Loughlin J, Gauvin L, Paradis G, Hanley J. Opportunities for student physical activity in elementary schools: a cross-sectional survey of frequency and correlates. Health education & behavior. 2006;33(2):215-32. DOI: 10.1177/1090198105277855

28. Lanningham-Foster L, Foster RC, McCrady SK, Manohar CU, Jensen TB, Mitre NG, Hill JO, Levine JA. Changing the school environment to increase physical activity in children. Obesity 2008; 16: 1849-1853. https://doi.org/10.1038/oby.2008.282

29. Ishii K, Shibata A, Sato M, Oka K. Recess physical activity and perceived school environment among elementary school children. International Journal of Environmental Research and Public Health. 2014; 11(7):7195-7206. https://doi.org/10.3390/ijerph110707195

CLINICAL SCIENCE

LESSONS FROM A MEDICAL STUDENT-RUN PUBLIC HEALTH JOURNAL CLUB- SURVEY STUDY

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Abstract

The aim of the study was to analyze student participation in a Public Health Journal Club focusing on their attitudes, self-perceived knowledge and skills in public health and research. Additionally, study aimed to determine whether there are differences in attitudes towards the importance of prevention, self-assessed understanding of research methodology, and frequency of reading papers in the groups before and after the Journal Club. We also included an analysis of the project implementation process. Materials and methods: Electronic surveys using Google Forms were designed to gather data from medical students participating in the Public Health Journal Club. Two surveys were created: a pre-assessment survey conducted before the sessions and a post-assessment survey for feedback afterward, providing a comparison of their views over time. Surveys assessed the attitudes, self-perceived knowledge, skills, and experiences of medical students in relation to public health, research, and participation in a Public Health Journal Club. Results: We observed that by participating in the Journal Club, students developed more positive attitudes toward public health and research, as well as improved knowledge and skills in these areas. We discovered that students had a higher self-assessed understanding of research methodology after participating in the Journal Club (p=0.023). Moreover, 81.8% of survey respondents reported that it was easier to interpret articles and 90.9% of respondents reported that they would like to take an elective course similar to our Journal Club. Conclusions: The described Journal Club was perceived as an effective educational activity by the participants and its re-use in different medical areas and specialties should be considered.

КЛИНИЧКИ ИСТРАЖУВАЊА

ЛЕКЦИИ ОД КЛУБ ЗА НАУЧНИ ТРУДОВИ ВО ЈАВНО ЗДРАВСТВО ВОДЕН ОД СТУДЕНТИ ПО МЕДИЦИНА - АНКЕТНА СТУДИЈА

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Клучни зборови: јавно здравство, студенти по медицина, клуб за научни трудови, образование, истражување

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Печатарски права: ©2025. Карла Крофлин, Карла Лужаиќ, Кристина Крстановиќ, Бруно Кораќ, Сања Мусиќ-Милановиќ. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Целта на оваа студија беше да се анализира учеството на студентите во Клубот за научни трудови во јавното здравство, со фокус на нивните ставови, самооценето знаење и вештини во областа на јавното здравство и истражувањето. Дополнително, студијата имаше за цел да утврди дали постојат разлики во ставовите кон значењето на превенцијата, самооценетото разбирање на истражувачката методологија и фреквенцијата на читање научни трудови во групите пред и по учеството во Клубот. Исто така, беше вклучена и анализа на процесот на спроведување на проектот. Материјали и методи: За собирање на податоци од студентите по медицина кои учествуваа во Клубот за научни трудови во јавното здравство беа дизајнирани електронски прашалници преку Google Forms. Создадени беа два прашалника: прашалник спроведен пред почетокот на сесиите и прашалник за нивните ставови по завршување, со што се овозможи споредба на нивните ставови со текот на времето. Прашалниците ги оценуваа ставовите, самооценетото знаење, вештините и искуствата на студентите по медицина во однос на јавното здравство, истражувањето и учеството во Клубот. Резултати: Учеството во клубот придонесе студентите да развијат позитивни ставови кон јавното здравство и истражувањето, како и подобрено знаење и вештини во овие области. Откривме дека студентите имаа повисоко самооценето разбирање на истражувачката методологија по учеството во Клубот (p=0,023). Дополнително, 81,8% од испитаниците изјавија дека полесно интерпретираат научни трудови, а 90,9% од нив изразија желба да посетуваат изборен предмет сличен на Клубот. Заклучоци: Клубот за научни трудови беше оценет како ефикасна образовна активност од страна на учесниците, па затоа треба да се разгледа можноста за негова примена во различни медицински области и специјалности.

Introduction

Medical students have a major potential for addressing public health issues and many develop their public health interventions. McLean et al. found that students felt like they had a role in public health advicegiving, but barriers to providing recommendations included their lack of knowledge[1]. Many studies were conducted about students' involvement in interventions during the COVID-19 pandemic, and a total of 91.7% of systematically reviewed articles found that medical students were willing to be involved in pandemic response[2]. Understanding research articles is essential for comprehending public health. Pruskil et al. found that 70% of students agreed that reading papers is challenging[3]. The majority of students agreed that the ability to critically evaluate literature is an important competency for physicians, but only 42.7% reported that their school provided adequate research training[4,5]. Journal clubs introduce critical thinking and participants often self-report increased carefulness in assessing articles[6,7]. During the COVID-19 pandemic, journal clubs were held online, while some valued a flexible approach, some sensed a loss of the social aspect of clubs.[8]

The Public Health Journal Club was developed by the Croatian Medical Students International Committee (CroMSIC) with the aim of motivating colleagues to actively discuss articles, public health challenges, and to join public health interventions. The Journal Club also aimed to help students improve critical thinking skills, public speaking skills, and knowledge of research methodology. The survey study presented here aims to bring new perspectives from the Public Health Journal Club to the wider public. We provide a detailed overview of the organization of our Public Health Journal Club. This survey study aimed to evaluate the involvement of students in a Public Health Journal Club, focusing on their attitudes, self-perceived knowledge, and skills related to public health and research. Additionally, it sought to assess any changes in students' perspectives on the importance of prevention, self-assessed understanding of research methods, and compare some answers before and after their participation in the Journal Club.

Materials and methods

Electronic surveys using Google Forms were designed to gather data from medical students participating in the Public Health Journal Club. Two surveys were created: a pre-assessment survey conducted before the sessions and a post-assessment survey for feedback afterward. The study participants were medical students who are members of CroMSIC. In December 2021, all CroMSIC members were invited to join the Public Health Journal Club, a new project of the Standing Committee on Public Health (SCOPH) in Zagreb, Croatia. All new Journal Club participants were invited to join our study with a link to the pre-assessment survey that was sent via email before each Club session. The post-assessment survey link was sent at the end of all Journal Clubs in June 2022 to everyone who participated. The purpose of the study was explained to the students and their consents were

obtained. Our Journal Club covered ten public health topics in ten one-hour discussions, as shown in Table 1. For each topic, three active participants, who volunteered via the official CroMSIC application, formed a small working group. During the one-month period, each of them read one paper and prepared a 10-minute presentation.

Table 1. Themes and discussion topics of the Public Health Journal Club sessions.

Journal Club topic	Specific themes from selected articles	Topics discussed in an open discussion after the articles were presented
Obesity	• BMI z-score[9] • Telephone survey for data collection, achieving behavior change with graphic imagery[10] • Socioeconomic limitations for health[11]	• Obesity as a cause of preventable death and cancer • California Sugar-Sweetened Beverages Tax Initiative • The vending machine ban in Slovenian schools
Lung cancer and smoking	• Emotionally evocative campaign, media and social marketing use in public health[12] • Medicaid in the USA, tobacco cessation pharmacotherapy, return on investment[13] • Croatian screening for lung cancer, radiation-induced cancers[14]	• Risks of e-cigarettes and their use as a quit-smoking aid • Tobacco Products Directive of the European Parlament • Artificial intelligence (AI) applications in computed tomography scans • Potential AI use for workload reduction in screening
Breast cancer	• Hazard ratio, association of mammography and the reduction of breast cancer mortality [(15)] • Students' involvement in public health[16] • Anastrozole in the reduction of breast cancer risk, randomized controlled trial [17]	• Importance of breast self-examination • Mammography risks and the use of breast ultrasound
Testicular and prostate cancer	• Interventions for testicular self-examination education[18] • Champion's Health Belief Model Scale[19] • Screening and prostate cancer mortality, rate ratio and incidence rate[20]	• National campaigns that promote testicular self-examination • Disadvantages of screening for prostate cancer • Mortality from prostate cancer in EU
Vaccination	• Types of rotavirus vaccines, WHO regions[21] • Test negative case-control design for vaccine effectiveness, odds ratio[22] • Epidemiology of measles, Andrew Wakefield, evidence of the MMR vaccine safety[23]	• The 1972 Yugoslav smallpox outbreak • 5C antecedents of vaccination • Anti-vaccine movements • "Our world in data" • European Center for Disease Control Virtual Academy

Sexually transmitted diseases	• Confounders and biases[24] • Sex education aspects[25] • Progession of therapy and care for HIV patients[26]	• Parent's education and involvement among their childrens' sex education • Ideas for HPV vaccination implementation
Social determinants of health	• Social determinants of obesity and tuberculosis2[7] • Epidemiology of Adverse Childhood Events (ACEs)[28] • Healthy cities, air pollution and health[29]	• Reductionism in clinical medicine • One Health and the Antibiotic Resistance • Local Particulate matter concentrations • Pediatric ACEs and Related Life Events Screener
Colorectal carcinoma	• Impact of AI on miss rate of colorectal neoplasia[30] • Impact of fecal immunochemical test on adenoma detection[31] • Health economic evaluation[32]	• Sigmoidoscopy in prevention of colorectal carcinoma • Colorectal cancer screening program in Croatia
Mental health	• Effects of suicide prevention videos, T-Value[33] • School success and mental health, correlation coefficient[34]	• Focus groups • Werther and Papageno effect • Reasons for not seeking professional help for psychological distress
Non-communicable diseases	• Polypill concept[35] • Impact of different social media apps and medications for lifestyle modifications[36,37]	• Improving health through social media • Adherence to recommendations

Presentations were prepared with the guidance of the local public health officer (LPO) and SCOPH assistants. A 30-minute online practice session was offered to all presenters one week before their scheduled presentations. Students who registered for passive participation received the articles by email one week ahead of the Club meeting. During the discussion, a moderator (LPO or assistant) provided open questions to add interactivity and emphasize learning outcomes. After each discussion, attendance was taken to obtain a total number of participants. Due to COVID-19, the first five sessions were held virtually. The project has been enrolled in the International Federation of Medical Students Associations "Medical Education Systems Program" in 2022.

Data was analyzed in Jamovi (11.3.0) statistical software. Descriptive statistics were used to calculate the frequencies of responses, and the alpha was always set a priori to 0.05. For comparing the groups before and after the Journal Club we used non-parametric tests due to small sample, and violation of both assumption of normality and equal variances. We tested the hypothesis that the Journal Club can increase the perceptions of the importance of prevention and self-assessed understanding of research methodology using Mann-Whitney U test. Due to small expected frequencies, we used the Fisher's test for testing the hypothesis that Journal Club can increase frequency of reading papers.

Results

A total of 87 students joined the Journal Club discussions (72.4% female and 27.6% male). Online discussions were attended by a mean of 28 students, while in-person discussions were attended by a mean of 12 students per meeting.

The pre-assessment survey was filled out by 35 students (response rate: 40.2%), and the post-assessment was filled out by 22 students (response rate: 25.3%). Most of the respondents were second-year (38.6%) and fourth-year students (33.33%). They were interested in clinical medicine specialties (89.47%), and 19.3% of respondents were also interested in public health specialties.

In order to analyze the students' attitudes, self-perceived knowledge and skills in the area of public health and research we presented data from the survey in Table 2 and Table 3. Data revealed that 77.1% of respondents had never attended a journal club and 88.6% thought that activities concerning scientific research should be of greater relevance in schools. The post-assessment revealed that 63.6% of respondents were active participants in the Journal Club and 54.5% of respondents joined four or more Club discussions. All respondents expressed that they would like to be a part of a similar project as this Journal Club in the future. Also, it is highly motivating that 90.9% of respondents would like to take an elective course that is similar to the Public Health Journal Club. 81.8% of respondents stated that they had a greater interest to start or join public health interventions after joining the Journal Club.

Table 2. Results obtained from survey questions that assessed the categories about attitudes towards public health and research.

ATTITUDES RELATED SURVEY QUESTIONS	
PRE-ASSESSMENT	35 total participants
Have you ever joined any Journal club discussion (in Croatia or abroad)?	
Yes **No**	8 (22.9%) 27 (77.1%)
I believe I haven't had enough opportunities to learn about conducting and designing scientific articles during medical school.	
1 - Strongly disagree **2 - Disagree** **3 - Neither agree nor disagree** **4 - Agree** **5 - Strongly agree**	1 (2.9%) 3 (8.6%) 6 (17.1%) 14 (40%) 11 (31.4%)
I think activities concerning scientific research should be of greater relevance in medical schools.	
1 - Strongly disagree **2 - Disagree** **3 - Neither agree nor disagree** **4 - Agree** **5 - Strongly agree**	0 (0%) 0 (0%) 4 (11.4%) 12 (34.3%) 19 (54.3%)
POST-ASSESSMENT	22 total participants

Were you an active participant (presenter) in the CroMSIC Journal Club?	
Yes No I wanted to be, but I couldn't register through the website application form	14 (63.6%) 5 (22.7%) 3 (13.6%)
How many sessions of our Journal Club did you attend?	
One, two, three Four or more	10 (45.5%) 12 (54.5%)
Would you like to join a similar Journal club in the future?	
Yes No	22 (100%) 0 (0%)
I would like to take an elective course in medical school that is similar to the Public Health Journal Club I attended.	
Yes No	20 (90.9%) 2 (9.1%)
After joining the Public Health Journal Club, I have a greater interest to start or join public health interventions.	
1 - Strongly disagree 2 - Disagree 3 - Neither agree nor disagree 4 - Agree 5 - Strongly agree	0 (0%) 1 (4.5%) 3 (13.6%) 5 (22.7%) 13 (59.1%)

Moreover, 71.4% of respondents have never written a scientific paper, and after Journal Club all respondents claimed that their critical thinking skills were sharpened. Also, 72.7% of participants believe that their knowledge of prevention and interventions expanded a lot more than before the Club. A total of 54.5% of participants claimed that they had learned enough about different research study designs during the Journal Club. Furthermore, 81.8% of respondents reported it was easier to read and interpret scientific papers than before and all active participants noted that presenting in the Journal Club improved their public speaking skills.

Table 3. Results obtained from survey questions that assessed the categories about self-perceived knowledge and skills in the area of public health and research

SELF-ASSESSED KNOWLEDGE AND SKILLS RELATED SURVEY QUESTIONS	
PRE-ASSESSMENT	35 total participants
Are you experienced in writing scientific papers (review articles, original research articles, or case reports)?	
Yes No	10 (28.6%) 25 (71.4%)
POST-ASSESSMENT	22 total participants
I think I expanded my knowledge about prevention and interventions in the Public Health Journal Club.	
It did not expand It expanded a little It expanded a lot	0 (0%) 6 (27.3%) 16 (72.7%)

I think I sharpened my critical thinking skills in Journal Club discussions.	
My skills did not sharpen	0 (0%)
My skills sharpened a little	10 (45.5%)
My skills sharpened a lot	12 (54.5%)
I think that I learned enough about different research study designs during the Journal Club	
1 - Strongly disagree	0 (0%)
2 - Disagree	0 (0%)
3 - Neither agree nor disagree	5 (22.7%)
4 - Agree	12 (54.5%)
5 - Strongly agree	5 (22.7%)
After participating in the Journal Club I find it easier to read and interpret scientific papers than before.	
1 - Strongly disagree	0 (0%)
2 - Disagree	0 (0%)
3 - Neither agree nor disagree	4 (18.2%)
4 - Agree	4 (18.2%)
5 - Strongly agree	14 (63.6%)
Presenting in the Journal Club improved my public speaking skills.	
1 - Strongly disagree	0 (0%)
2 - Disagree	0 (0%)
3 - Neither agree nor disagree	0 (0%)
4 - Agree	5 (38.5%)
5 - Strongly agree	8 (61.5%)

In order to review the project implementation process, we presented all the data in Table 4. 77.3% of the students attended the Journal Club discussions both online and in-person. A high percentage of participants, 86.4%, strongly agreed that they were easily communicating opinions because we were all colleagues in Journal Club discussions.

Table 4. Results obtained from survey questions that assessed the categories about the Public Health Journal Club project implementation process.

PROJECT IMPLEMENTATION RELATED SURVEY QUESTIONS	
PRE-ASSESSMENT	22 total participants
In which format were you attending the Journal Club discussions?	
Just online	1 (4.5%)
Just in-person	4 (18.2%)
Both online and in-person	17 (77.3%)
If you were joining both online and in-person, what was more beneficial for you?	
Online	1 (5.6%)
In-person	14 (77.8%)
Both were the same	3 (16.7%)
If you have answered yes to the previous question (see Table 2), in which year would you suggest students take such an elective course?	

First	1 (5%)
Second	4 (20%)
Third	4 (20%)
Fourth	5 (25%)
Fifth	6 (30%)
I believe we were easily expressing our opinions because we were all colleagues in Journal Club discussions (only students joined).	
1 - Strongly disagree	0 (0%)
2 - Disagree	0 (0%)
3 - Neither agree nor disagree	1 (4.5%)
4 - Agree	2 (9.1%)
5 - Strongly agree	19 (86.4%)
I think that professors should be present during the Journal Club.	
1 - Strongly disagree	4 (18.2%)
2 - Disagree	12 (54.5%)
3 - Neither agree nor disagree	3 (13.6%)
4 - Agree	3 (13.6%)
5 - Strongly agree	0 (0%)
Did the Journal Club fulfill your expectations?	
Yes	16 (72.7%)
No	0 (0%)
I didn't have any expectations	6 (27.3%)

Observing the values before and after participating in Journal Club in Table 5, no statistically significant difference was observed in the perception of the importance of prevention among the respondents (p=0.269; Mann-Whitney U test). The understanding of research methodology showed statistically significant differences between the two surveys (p=0.023; Mann-Whitney U test). Analysis showed that the frequency of reading scientific papers by respondents before and after participating in the Club was changed. There was a noticeable increase in the share of respondents who started reading scientific papers weekly after participation (from 11.4% to 31.8%) and a significant drop (from 17.1% to 9.1%) in the share of those who never read papers or did so several times a year (p=0.166; Fisher's test).

Table 5. Differences in attitudes towards the importance of prevention and differences in self-assessed understanding of research methodology in the groups before and after the Journal Club.

Survey question	Group	Number of the respondents	Mean	Median	SD	SE
Prevention is very important to me	Pre-assessment	35	4.94	5.00	0.23	0.03
	Pre-assessment	22	5.00	5.00	0.00	0.00
I understand scientific methodology well	Pre-assessment	35	3.37	3.00	1.00	0.16
	Pre-assessment	22	3.95	4.00	0.78	0.16

Discussion

Our Journal Club introduced an innovative method for bringing public health topics closer to medical students. We observed that by participating in the Journal Club, medical students developed more positive attitudes toward public health and research topics, as well as improved knowledge and skills in these areas. We discovered a statistically significant difference between the pre- and post-intervention groups, with the post-intervention group having a higher self-assessed understanding of research methodology. A higher frequency of reading papers and a more positive perception of the importance of prevention were not statistically significant. This was most likely due to the fact that nearly half of those who completed the post-evaluation joined the Journal Club three times or less. Our research showed that students can organize quality educational content for one another. Similarly, authors from Saudi Arabia found out that journal club participants with varying academic levels enhanced collaborative communication and assisted in clarifying and explaining concepts[38]. Furthermore, one of the advantages of joining the Club was the opportunity to meet new colleagues during the pandemic that impacted networking events. Journal Club discussions were a place where colleagues exchanged ideas and collaborated with each other. Due to the preventative measures for COVID-19, half of the Journal Club sessions were held in the online format and half in person. More students participated in online sessions. This could be attributed to inconvenient traveling that was required and scheduling conflicts. Lizer et al. concluded that a journal club effectively motivates critical reading and helps teach epidemiology and biostatistics to physicians in training[39]. Consequently, we tried to follow these findings and a great number of our participants were content with our methodology and statistics explanations.

There were some limitations to our study. For instance, we were unable to match the respondent's results from the pre- and the post-assessment survey. We compared two respondents' groups without knowing if they filled out both surveys. A sample size was one of the reasons for using non-parametric tests which resulted in less statistical power. Lastly, our study results were based on self-perceived assessments and in the future more follow-up studies could be conducted.

Conclusions

Strong health systems require more public health informed professionals, so public health knowledge should be provided to medical students in the most practical way possible. Most students will become clinicians and each clinician is an important health advocate. Understanding the importance of advocacy and health policies can be crucial for influencing decision-makers and delivering better healthcare. The described Public Health Journal Club was perceived as an effective educational activity by the participants and its re-use in different medical areas and specialties should be considered.

References

1. McLean S, Charlesworth L, May S, Pollard N. Healthcare students' perceptions about their role, confidence and competence to deliver brief public health interventions and advice. BMC Med Educ. 2018;18(1):1–9. doi: 10.1186/s12909-018-1224-0
2. Martin A, Blom IM, Whyatt G, Shaunak R, Viva MIF, Banerjee L. A rapid systematic review exploring the involvement of medical students in pandemics and other global health emergencies. Disaster Med Public Health Prep. 2022;16:360–372. doi: 10.1017/dmp.2020.315
3. Pruskil S, Burgwinkel P, Georg W, Keil T, Kiessling C. Medical students' attitudes towards science and involvement in research activities: A comparative study with students from a reformed and a traditional curriculum. Med Teach. 2009;31(6). doi: 10.1080/01421590802637925
4. Ratte A, Drees S, Schmidt-Ott T. The importance of scientific competencies in German medical curricula - The student perspective. BMC Med Educ. 2018;18(1). doi: 10.1186/s12909-018-1257-4
5. Funston G, Piper RJ, Connell C, Foden P, Young AMH, O'Neill P. Medical student perceptions of research and research-oriented careers: An international questionnaire study. Med Teach. 2016;38(10):1041–1048. doi: 10.3109/0142159X.2016.1150981
6. Lucia VC, Swanberg SM. Utilizing journal club to facilitate critical thinking in pre-clinical medical students. Int J Med Educ. 2018; 9:7–8. doi: 10.5116/ijme.5a46.2214
7. Nahai F. Are Journal Clubs Worth the Effort? Aesthet Surg J. 2020;40:584–585. doi: 10.1093/asj/sjz359
8. Mark I, Sonbol M, Abbasian C. Running a journal club in 2020: reflections and challenges. BJPsych Bull. 2021;45(6):339–342. doi: 10.1192/bjb.2020.121
9. Economos CD, Hyatt RR, Must A, et al. Shape Up Somerville two-year results: A community-based environmental change intervention sustains weight reduction in children. Prev Med. 2013;57(4):322–327. doi: 10.1016/j.ypmed.2013.06.001
10. Morley B, Niven P, Dixon H, et al. Association of the LiveLighter mass media campaign with consumption of sugar-sweetened beverages: Cohort study. Health Promot J Aust. 2019;30(S1):34–42. doi: 10.1002/hpja.244
11. Stacey N, Edoka I, Hofman K, Swart EC, Popkin B, Ng SW. Changes in beverage purchases following the announcement and implementation of South Africa's Health Promotion Levy: an observational study. Lancet Planet Health. 2021;5(4):e200–208. doi: 10.1016/S2542-5196(20)30304-1
12. McAfee T, Davis KC, Alexander RL, Pechacek TF, Bunnell R. Effect of the first federally funded US antismoking national media campaign. Lancet. 2013;382(9909):2003–2011. doi: 10.1016/S0140-6736(13)61686-4
13. Richard P, West K, Ku L. The return on investment of a medicaid tobacco cessation program in Massachusetts. PLoS One. 2012;7(1). doi: 10.1371/journal.pone.0029665
14. van Meerbeeck JP, Franck C. Lung cancer screening in Europe: where are we in 2021? Transl Lung Can-

cer Res. 2021;10(5):2407–2417. doi: 10.21037/tlcr-20-890

15. Duffy SW, Vulkan D, Cuckle H, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol. 2020;21(9):1165–1172. doi: 10.1016/S1470-2045(20)30398-3

16. Kovačević J, Jureša V, Musil V, Zombori D. Rak Dojke I Probir Na Rak Dojke Javnozdravstvena Intervencija Za Povećanje Obuhvata Žena Mamografskim Pregledom U Sklopu Nacionalnog Programa Ranog Otkrivanja Raka Dojke. Acta Med Croatica. 2018;72:115–124.

17. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020;395(10218):117–122. doi: 10.1016/S0140-6736(19)32955-1

18. Akar ŞZ, Bebiş H. Evaluation of the effectiveness of testicular cancer and testicular self-examination training for patient care personnel: Intervention study. Health Educ Res. 2014 Dec 1;29(6):966–976. doi: 10.1093/her/cyu055

19. Thornton CP. Best Practice in Teaching Male Adolescents and Young Men to Perform Testicular Self-Examinations: A Review. J Pediatr Health Care. 2016 Nov 1;30(6):518–527. doi: 10.1016/j.pedhc.2015.11.009

20. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384(9959):2027–2035. doi: 10.1016/S0140-6736(14)60525-0

21. Aliabadi N, Antoni S, Mwenda JM, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the Global Rotavirus Surveillance Network. Lancet Glob Health. 2019;7(7):e893–903. doi: 10.1016/S2214-109X(19)30207-4

22. Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants. JAMA. 2022;327(7):639–651. doi: 10.1001/jama.2022.0470

23. DeStefano F, Shimabukuro TT. The MMR Vaccine and Autism. Annu Rev Virol. 2019;6:585–600. doi: 10.1146/annurev-virology-092818-015515

24. Gerend MA, Murdock C, Grove K. An intervention for increasing HPV vaccination on a university campus. Vaccine. 2020;38(4):725–729. doi: 10.1016/j.vaccine.2019.11.028

25. Goldfarb ES, Lieberman LD. Three Decades of Research: The Case for Comprehensive Sex Education. J Adolesc Health. 2021;68:13–27. doi: 10.1016/j.jadohealth.2020.07.036

26. Ford N, Patten G, Rangaraj A, Davies MA, Meintjes G, Ellman T. Outcomes of people living with HIV after hospital discharge: a systematic review and meta-analysis. Lancet HIV. 2022;9(3):e150–159. doi: 10.1016/S2352-3018(21)00329-5

27. Greene JA, Loscalzo J. Putting the Patient Back Together — Social Medicine, Network Medicine, and the Limits of Reductionism. N Engl J Med. 2017;377(25):2493–2499. doi: 10.1056/nejmms1706744

28. Peek-Asa C, Mujkić A. Prevalence, impact, and approaches to prevention for global adverse childhood events. Paediatria Croatica. 2015;59(Supl 1):145–151.

29. Guan WJ, Zheng XY, Chung KF, Zhong NS. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. Lancet. 2016;388(10054):1939–1951. doi: 10.1016/S0140-6736(16)31597-5

30. Wallace MB, Sharma P, Bhandari P, et al. Impact of Artificial Intelligence on Miss Rate of Colorectal Neoplasia. Gastroenterology. 2022;163(1):295-304.e5. doi: 10.1053/j.gastro.2022.03.007

31. Nwankwo EC, Lines J, Trehan S, et al. Improving Adenoma Detection Rates: The Role of the Fecal Immunochemical Test. Cureus. 2021;13(4). doi: 10.7759/cureus.14382

32. Cox B, Sneyd MJ, Hingston G, McBride D, Bagshaw PF. Enhancing bowel screening: Preventing colorectal cancer by flexible sigmoidoscopy in New Zealand. Public Health. 2020;179:27–37. doi: 10.1016/j.puhe.2019.09.021

33. Braun M, Till B, Pirkis J, Niederkrotenthaler T. Effects of suicide prevention videos developed by and targeting adolescents: a randomized controlled trial. Eur Child Adolesc Psychiatry. 2021; 1-11. doi: 10.1007/s00787-021-01911-6

34. Vulić-Prtorić A, Lončarević I. Školski uspjeh i mentalno zdravlje: Od relacija do intervencija. Napredak. 2016; 157(3):302-324.

35. Yusuf S, Joseph P, Dans A, et al. Polypill with or without Aspirin in Persons without Cardiovascular Disease. N Engl J Med. 2021;384(3):216–228. doi: 10.1056/nejmoa2028220

36. De La Garza H, Maymone MBC, Vashi NA. Impact of social media on skin cancer prevention. Int J Environ Res Public Health. 2021;18. doi: 10.3390/ijerph18095002

37. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-4. doi: 10.1056/NEJMoa012512

38. Aljumaa R, Elmokattaf R, Aljumaa M, et al. Assessing Medical Students' Perception of Implementing Journal Club Activities: A Qualitative Study. Cureus. 2023;15(11):e48726. doi: 10.7759/cureus.48726

39. Linzer M, Brown JT, Frazier LM, DeLong ER, Siegel WC. Impact of a medical journal club on housestaff reading habits, knowledge, and critical appraisal skills. A randomized control trial. JAMA. 1988;260(17):2537-41. PM

PUBLIC HEALTH

ASSESSMENT OF DISEASE BURDEN CAUSED BY BIOLOGICAL AGENTS ASSOCIATED WITH UNSAFE FOOD IN THE REPUBLIC OF NORTH MACEDONIA

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Key words: burden, biological agents, unsafe food, YLD, DALY

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Abstract

Diseases associated with unsafe food are common and cause significant public health and socioeconomic impact globally. The aim of the paper is to determine the burden of infections caused by biological agents at the national level and to determine the public health and economic impact. Material and methods: data from the national database of infectious diseases for 2019 were used, incidence, YLL, YLD, DALY and economic losses were determined. Results: In 2019, 7682 patients with diseases caused by biological agents were registered, of which 3755 or 48.9% were male patients and 3927 or 51.10 % were female patients. The most represented age group are people aged 6-15 (211 patients). The highest number of cases were registered in Skopje with 312 cases (32.8%). DALY is 1417,328 or 68.25 DALY per 100 000 population. The economic burden is 472 751 172 denars or 7 687 011 €. Conclusion: A better understanding of the true burden of foodborne disease is important for food safety policy making and decision making

ЈАВНО ЗДРАВЈЕ

ПРОЦЕНКА НА ОПТОВАРУВАЊЕ СО БОЛЕСТИ ПРЕДИЗВИКАНИ ОД БИОЛОШКИ АГЕНСИ ПОВРЗАНИ СО НЕБЕЗБЕДНА ХРАНА ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Цитирање: Костова А, Ристовска Г, Гудева Никовска Д. Проценка на оптоварување со болести предизвикани од биолошки агенси поврзани со небезбедна храна во Република Северна Македонија Арх Ј Здравје 2025;17 (1) 26-39.

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Клучни зборови: оптовареност,биолошки агенси, небезбедна храна,YLD, DALY

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Печатарски права: ©2025. Анета Костова, Гордана Ристовска, Данче Гудева Никовска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Болестите поврзани со небезбедна храна, се чести и предизвикуваат значително јавно здравствено и социоекономско влијание на глобално ниво. Цел на трудот е да се одреди оптоварувањето со болести предизвикани со биолошки агенси на национално ниво и да се утврди јавно здравственото и економското влијание. Материјал и методи: користени се податоци од националната датабаза на заразни болести за 2019 година, одредена е инциденца, YLL, YLD, DALY и економските губитоци. Резултати: Во 2019 година регистрирани се 7682 заболени лица од болести предизвикани од биолошки агенси, од кои 3755 или 48,9% пациенти од машки пол и 3927 или 51,1% пациенти од женски пол. Најзастапена возрасна група се лицата од 6-15 години (211 пациенти). Највисок број на случаи се регистрирани во Скопје со 312 случаи (32,8%). DALY изнесува 1417,328 или 68,25 DALY на 100 000 население. Економското оптоварување изнесува 472 751 172 денари или 7 687 011 €. Заклучок: Подоброто разбирање на вистинската оптовареност на болестите што се пренесуваат преку храна е важно за креирање на политиката за безбедност на храна и донесување одлуки.

Introduction

The concept of burden of disease assessment was developed in the 1990s by the Harvard School of Public Health, the World Bank and the WHO to describe death and loss of health due to disease, injury and risk factors for all regions of the world[1] While the burden of disease can be expressed using a variety of indicators, such as incidence, mortality, societal costs, and aggregate measures of population health, this study introduced a new metric, Disability Adjusted Life Years (DALY), which combines information on morbidity and mortality caused by diseases. The DALY is now the most widely used public health metric for disease burden studies and the key measure in the Global Burden of Disease studies[2]

The first estimates of the burden of disease associated with unsafe food, measured in Disability Adjusted Life Years (DALYs), were published in 2000, focusing on a single foodborne pathogen in the Netherlands[3]. In 2015, the World Health Organization (WHO) released the first global DALY estimate for the burden of foodborne diseases. Several countries, including the Netherlands, Japan, Denmark, Belgium, and the United States[4], have since conducted studies on foodborne disease burden, primarily targeting microbial agents.

Low-income countries are beginning to address knowledge gaps in this area. For instance, Rwanda[5] has estimated the incidence of foodborne diseases using syndromic surveillance data, and the Caribbean Burden of Disease Study[6] has assessed the prevalence and incidence of acute gastroenteritis and specific foodborne pathogens across nine countries. These initiatives represent initial steps towards comprehensive national disease burden studies.

The initial step in each national study was to identify food supply hazards relevant to the pilot country. Lists of hazards and associated diseases that were compiled, with each country adding predicted hazards significant from their perspective.[7] Available information on the incidence of diseases associated with these hazards and the prevalence of the hazards in the food supply was then collected. These data were summarized, and the disease burden was attributed to specific foods based on the available data.[8]

The Global Burden of Disease Study 2010, conducted by the Institute for Health Metrics and Evaluation in Seattle USA, encompasses a broad spectrum of diseases and injuries, providing country-specific estimates.[9] National studies on food-related diseases, promoted by WHO and Foodborne Disease Burden Epidemiology Reference Group (FERG), incorporate situation analysis that considers the national context, including the existing national food control system.[10]

National studies of the burden of food-related disease, particularly in developing countries, now have the opportunity to address data gaps and assign etiology and attribution to the incidence of food-related disease, by leveraging data from the WHO initiative and local sources. [11] Information on the burden of disease associated with unsafe food should be a core component to a systematic approach to food safety, as advocated by the Codex risk management framework.[12] Such an approach can enhance public health and facilitate trade.

Estimating the burden of disease as-

sociated with unsafe food is challenging because few diseases can be definitively linked to food, with connections often identified only during outbreak situations.[13] Although not all acute gastrointestinal illnesses are foodborne and foodborne illnesses do not always result in acute gastroenteritis, food remains a significant vector for pathogens that cause acute gastroenteritis.[14]

Diseases associated with unsafe food are prevalent and have significant public health and socioeconomic impact globally.[15] The World Health Organization (WHO) estimated that, in 2010, 22 foodborne enteric pathogens have caused two billion illnesses, over one million deaths, and 78.7 million DALYs. While intestinal disease often manifests as a self-limiting AGI, presenting as diarrhea or vomiting, they can lead to severe illness and even death[16].

The aim of this study is to quantify the national burden of infections caused by biological agents related to unsafe food and to assess their public health and economic impacts. Sub-objectives of the paper are:

- To determine the incidence and morbidity of infections caused by biological agents. related to unsafe food during 2019;
- To quantify the burden of these infections using DALY indicator
- To assess the economic impact of infections caused by biological agents related to unsafe food.

Materials and methods

Data from the national database for infectious diseases, maintained by the Institute of Public Health of the Republic of North Macedonia was utilized for the year 2019. Family physicians are mandated to complete a notification form for each occurrence of an infectious disease among patients. These forms are submitted to the Centers for Public Health, which then forward the information to the Public Health Institute of North Macedonia.

This study employs the DALY measure, which integrates data on morbidity, mortality and disability caused by diseases. DALY is a more comprehensive metric than incidence or prevalence rate; it is now the most widely used public health metric for disease burden studies, serving as the key measure in the Global Burden of Disease (GBD) Study.

DALY quantifies the health gap by measuring the years of healthy life lost due to disease or risk factors. It is calculated by summing the years of life lost due to premature mortality (YLL) and the years lived with disability (YLD), adjusted for the severity of the disability:

DALY=YLL+YLD

YLL is the product of the number of deaths (M) and the average remaining life expectancy (RLE) at the time of death:

YLL=M x RLE

The 2010 GBD study introduced a prevalence based approach to calculating burden of disease. This method assesses the current burden of disease as a consequence of past events, evaluating the health status of a population at a specific point in time and attributing prevalent diseases to initial events that occurred previously. While the definition of YLL remains consistent with the incidence-based approach, YLD is defined as the prod-

uct of the number of prevalent cases (P) and the disability weight (DW). The disability weight reflects the reduction in health-related quality of life on a scale from 0 (no effect on full health) to 1 (death).

YLDprev=P x DW

To estimate YLL, the use of a standard life table is recommended, to reflect the ideal life expectancy, based on the lowest possible mortality given the currently available data. Various standard life tables have been developed for the WHO Global Health Assessment (GHA) and GBD studies by the Institute for Health Metrics and Evaluation (IHME).

However, for this study, we will utilize the life table specific to the Republic of North Macedonia. The weight of each health outcome is represented by disability weights (DW), which range from 0 to 1, where 0 represents full health and 1 represents death. DW can be interpreted as a proportional decrease in good health due to an adverse health condition.

The study used WHO methodology.11

Given the difficulty of making detailed estimates of the value of YLL or YLD, a frequently used shortcut is to use a country's per capita gross domestic product (GDP) as a measure of lost productivity. For every year lost to illness, disability or premature death, the country loses the economic output associated with that year. Foodborne disease is therefore represented as a drain on the country's productivity. The calculation is represented by the following formula:

$VPi = Bi \times Yi$

where VPi is the value of productivity losses associated with foodborne diseases in country i; Bi is the total DALY burden of foodborne diseases in country i; and Yi is GDP per capita for country i. We will express this value in local currency (Denars) or in Euros to allow comparison between countries.

Chi-square one- or two-sample test were used to compare specific features between two groups. Cramer'V was used to determine the association between two nominal variables.

Results

In 2019, 7682 cases of diseases related to unsafe food were registered. 12 foodborne diseses were reported to IPH, in the database of infectious diseases, representing alimentary diseases.

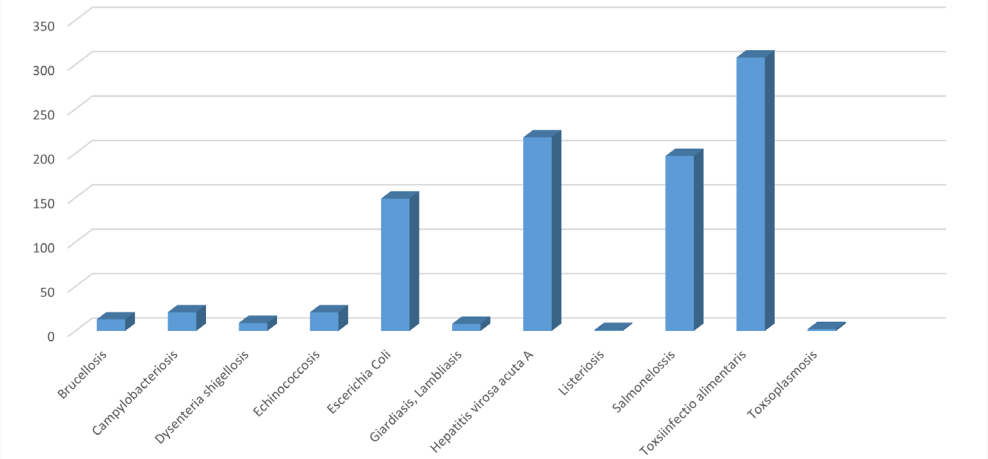


Chart 1: Total number of diseases related to unsafe food

From the total number of food-borne diseases, the largest number of diseases are Enterocolitis with 6735 cases, then Bacterial alimentary infections and intoxications with 308 cases, Viral Hepatitis A with 218 cases, Salmonellosis with 197 cases, Echinococcosis with 21 cases Campylobacteriosis with 21 cases, Brucellosis with 13 cases, Shigellosis with 9 cases and Giardiasis with 8 cases. The lowest number of foodborne diseases is Listeriosis with 1 case, followed by Toxoplasmosis with 2 cases. The structure of diseases related to unsafe food is shown in Chart 1.

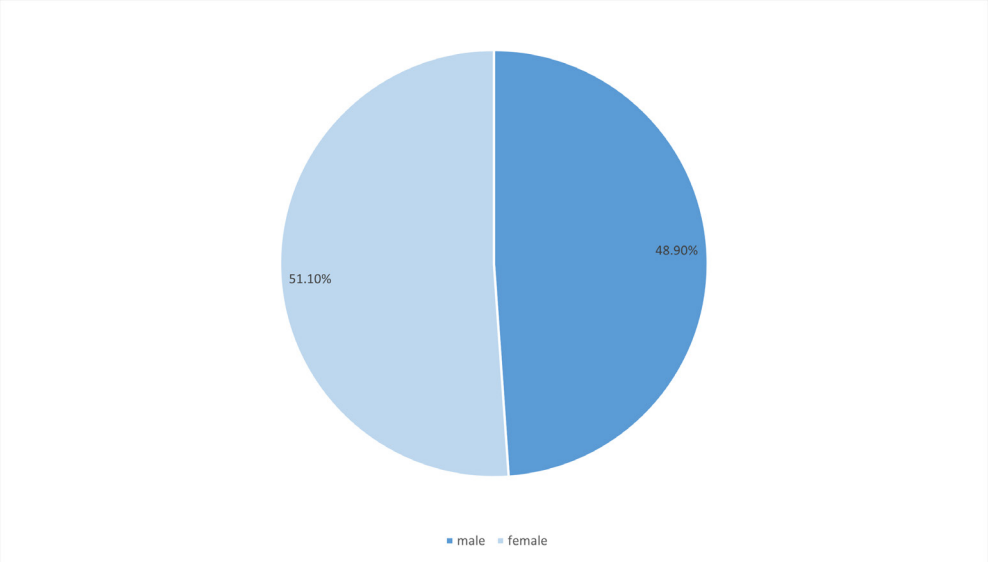


Chart 2: Structure by gender of patients with diseases related to unsafe food

The analysis included 7682 patients suffering from diseases related to unsafe food, of which 3755 or 48.90% were male patients and 3927 or 51.10% were female patients (Graph 2)

The gender analysis did not find statistically significant difference between male and female patients (Chi-square:3.336; df=1; p=0.068)

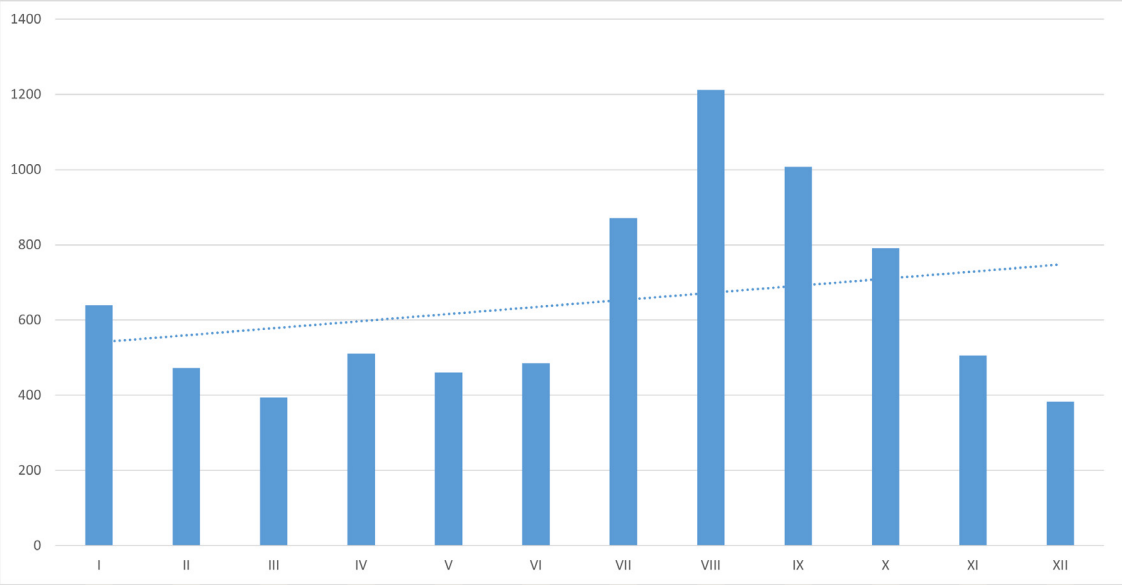


Chart 3: Seasonal occurrence of foodborne diseses by month

In terms of seasonal changes, the largest number of diseases occurred in the month of August with 1212 cases, in the month of September with 1007 cases, in the month of July with 871 cases. The lowest number of cases occurred in the month of December with 383 cases, and then in the month of March with 394 cases. The seasonal occurrence of BNH is shown in Chart 3. The graphic display indicates an increasing trend of diseases by month for 2019.

Data on Enterocolitis was not analyzed, as this diagnosis was not entered into the database of the Public Health Institute.

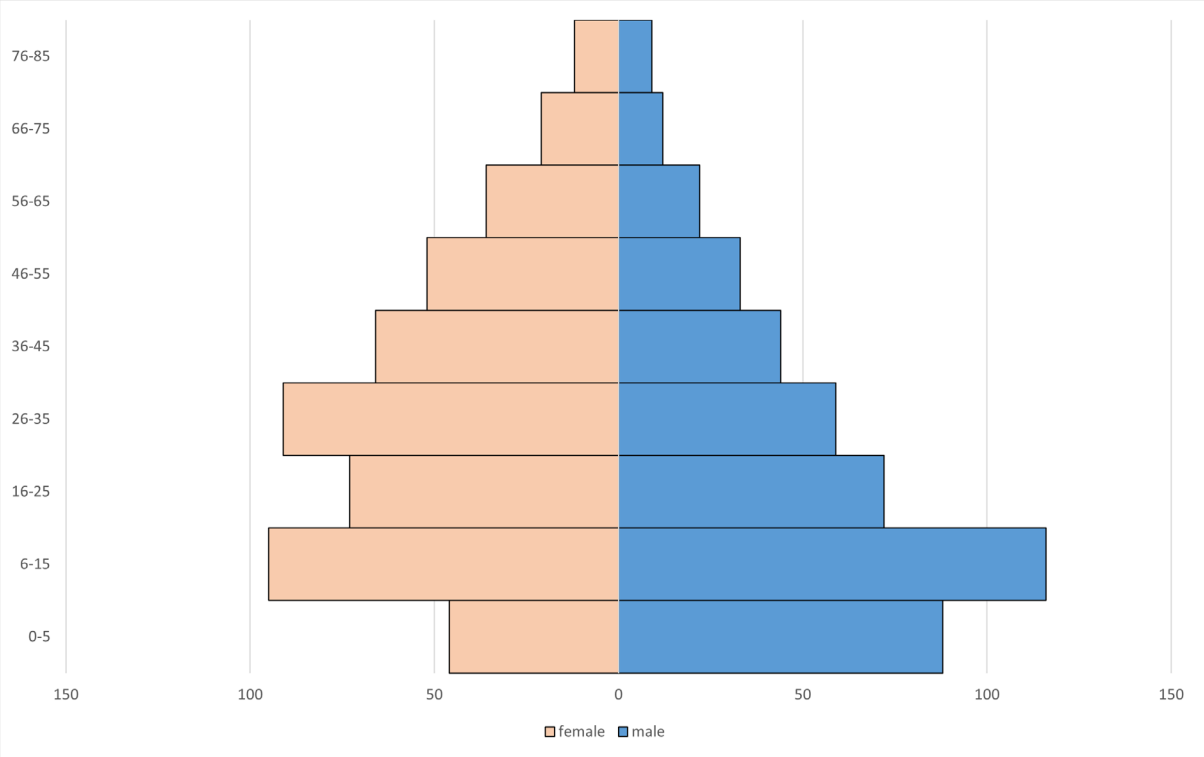


Chart 4: Presentation of the age pyramid for foodborne disesases

In terms of age, the most represented group for female patients is 6-15 years old (95 patients), then 26-35 years old (91 patients) and 16-25 years old (73 patients). The least represented age group for female patients is 76-85 years (12 patients), followed by the age group 66-75 years (21 patients). Regarding male patients, the most represented age group is from 6-15 years (116 patients), followed by the age group from 0-5 years (88 patients). The least represented age group for male patients is 76-85 years (9 patients), followed by the age group 66-75 years (12 patients). The structure by age groups of patients is shown in Chart 4.

In 2019, the highest number of cases with foodborne diseases were registered in Skopje with 312 cases (32.8%), followed by Bitola with 122 cases (12.8%) and Kumanovo with 112 cases (11.8%). In the same period, the lowest number of cases were registered in Debar and Pehčevo with only one case (0.1%). The graphic presentation of cases of diseases related to unsafe food by municipality is presented in Graph 5.

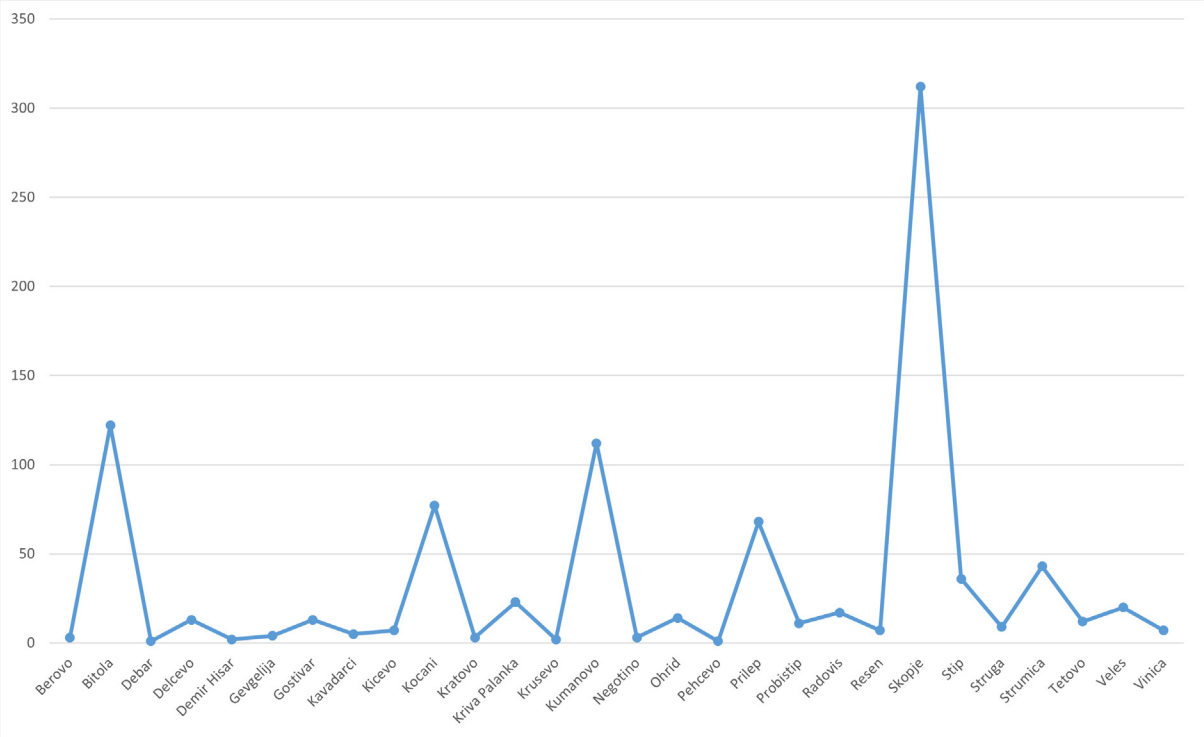


Chart 5: Presentation of foodborne diseases cases by municipalities

Within the analysis of the structure of patients in relation to employment status, it was observed that 283 (29.8%) patients are employed, 231 (24.3%) are students, 162 (17.0%) are unemployed, 151 are children. (15.9%), pensioners are 58 (6.1%), housewives are 38 (4.0%), primary and secondary school students are 16 (1.7%) and refugees are 10 (1.1%).

The difference between persons with foodborne diseases in terms of employment status shows statistically significant difference between groups (Chi-square:632.952; df=7; p<0.001)

Table 1: Hospitalization for foodborne diseases according to gender

		hospitalization		Total
		yes	no	
Gender	male	144 (15.2%)	311 (32.8%)	457 (48.0%)
	female	223 (23.5%)	269 (28.4%)	492 (52.0%)
Total		367 (38.8%)	580 (61.2%)	947 (100%)

Regarding hospitalization, the analysis showed that male patients were hospitalized in 144 (15.2%) cases, while female patients were hospitalized in 223 (23.5%) cases. Male patients were not hospitalized in 311 (32.8%) cases, while female patients were not hospitalized in 269 (28.4%) cases (Table 1)

The analysis showed statistically significant difference between patient gender and hospitalization (Chi-square: 18.630; df=1; p<0.001).

The analysis showed high association between patient gender and hospitalization (Cramer's V:0.714; p<0.001).

Table 2: Hospitalization for foodborne diseases by employment status

		Hospitalization		Total
		Yes	no	
Work status	Child	47 (5.0%)	104 (11.0%)	151 (15.9%)
	Pupil	66 (7.0%)	164 (17.3%)	230 (24.3%)
	Student	8 (0.8%)	8 (0.8%)	16 (1.7%)
	Worker	120 (12.7%)	162 (17.1%)	282 (29.8%)
	Unemployed	68 (17.2%)	94 (9.9%)	162 (17.1%)
	Housewife	20 (2.1%)	18 (1.9%)	38 (4.0%)
	Pensioner	28 (3.0%)	30 (3.2%)	58 (6.1%)
	Refugee	10 (1.1%)	0	10 (1.1%)
Total		367 (38.8%)	580 (61.2%)	947 (100%)

Regarding hospitalization by employment status, the analysis showed that the largest number of hospitalized patients were employed 120 (12.7%), unemployed 68 (17.2%), students 66 (7.0%) The smallest number of hospitalized patients were students in primary and secondary school 8 (0.8%). While students were not hospitalized in 164 (17.3%) cases, workers were not hospitalized in 162 (17.1%) cases and unemployed patients were not hospitalized in 94 (9.9%) cases. (Table 2).

The analysis by groups showed statistically significant difference between the structure of patients by employment status and hospitalization (Chi-square: 37.884; df=7; p<0.001). The analysis showed moderate association between the structure of patients by employment status and hospitalization (Cramer's V: 0.201; p<0.001).

Data analysis showed statistically significant difference between laboratory-confirmed diagnosis and hospitalization among patients with food-related illnesses. (Chi-square:16.038; df=1; p<0.001). The analysis showed low association between laboratory-determined diagnosis and hospitalization (Cramer's V: 0.130; p<0.001).

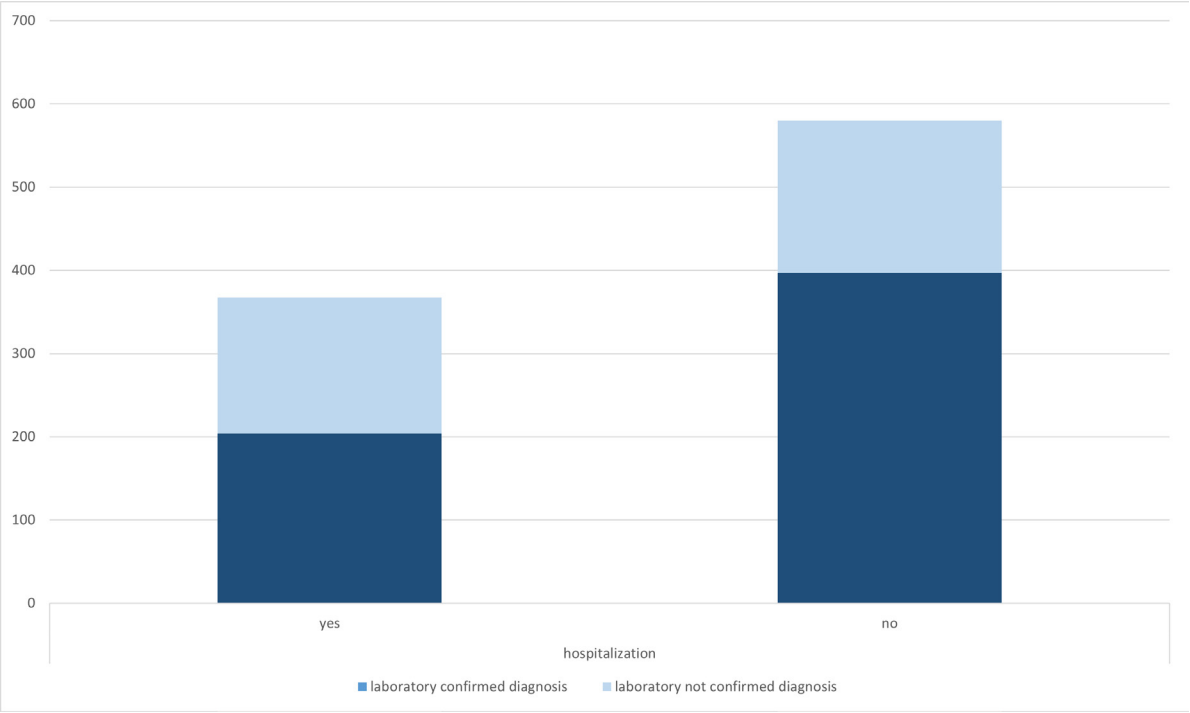


Chart 6: Presentation of patients with total diseases related to unsafe food in relation to laboratory-confirmed diagnosis and hospitalization

Data analysis showed statistically significant difference between clinically confirmed diagnosis and hospitalization among patients with food-related illnesses (Chi-square: 21.110; df=1; $p<0.001$). The analysis showed low association between clinically confirmed diagnosis and hospitalization (Cramer's V: 0.149; $p<0.001$).

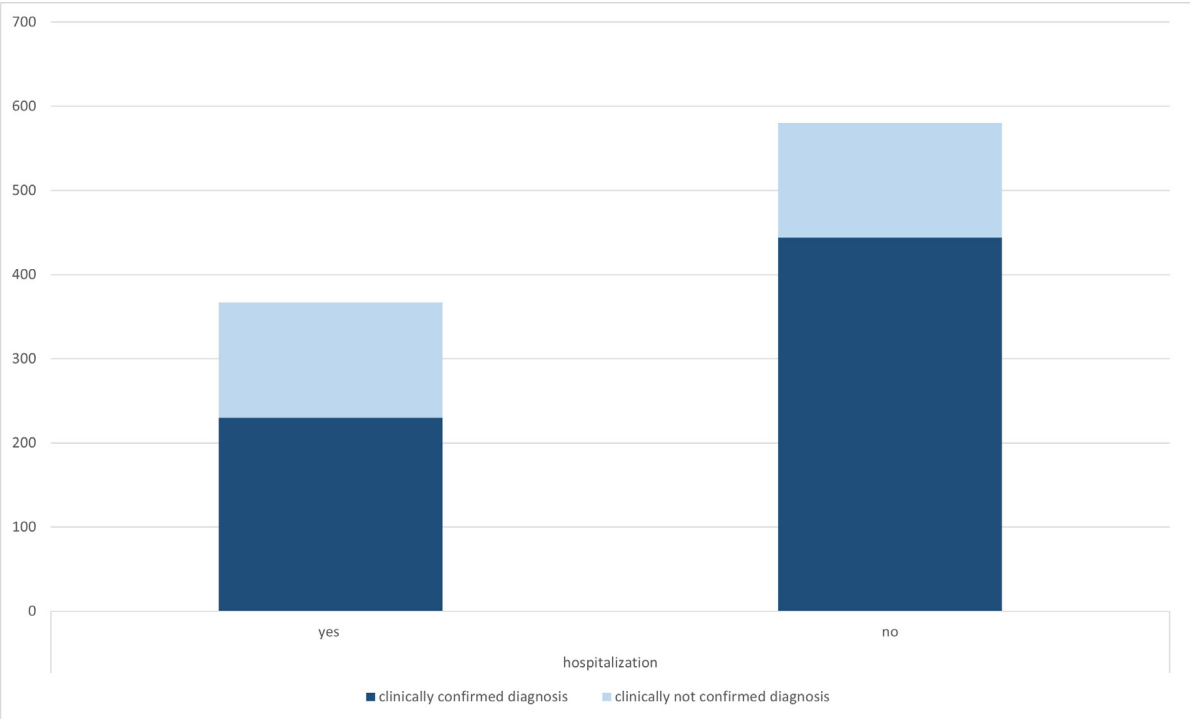


Chart 7: Presentation of patients with foodborne diseases related to unsafe food in relation to clinically confirmed diagnosis and hospitalization

Pathogen	Number of cases	Morbidity Per 100,000 population	YLL	YLD	DALY	DALYs per 100 000 population
Bacterial alimentary infections and intoxications	308	14,83	0	58	58	2,8
Brucellosis	13	0,63	0	1,404	1,404	0,068
Virus Hepatitis A	218	10,5	0	23,54	23,54	1,133
Enterocolitis	6735	324,38	0	1266,18	1266,18	60,97
Echinococcosis	21	1,01	0	4,032	4,032	0,194
Escherichia coli infections	149	7,18	0	11,03	11,03	0,53
Campylobacteriosis	21	1,01	0	2,12	2,12	0,102
Listeriosis	1	0,05	29,3	0,210	29,51	1,42
Salmonellosis	197	9,49	0	19,9	19,9	0,96
Toxoplasmosis	2	0,096	0	0,11	0,11	0,005
Giardiasis	8	0,39	0	0,592	0,592	0,0285
Shigellosis	9	0,433	0	0,91	0,91	0,0438
Total	**7682**	**370,08**	**29,3**	**1388,03**	**1417,328**	**68,25**

DALYs and economic burden of foodborne diseases

The morbidity rate of total diseases related to unsafe food is 370.0 per 100 000 population

Mb = (O/S) x K = (7682/2076255) x 100 000 = 370.0 (5)

The sex-specific morbidity rate is 378.8 per 100,000 population for women and 361.1 per 100,000 population for men.

Mbfemales = (3927 / 1036736) x 100 000 = 378.8

Mbmales = (3755 / 1039958) x 100,000 = 361.1

The incidence rate is 3.7 per 1000 population

Incidence rate = (7682/2076255) x 1000 = 3.7

DALY = YLL + YLD

ΣDALY = 58 + 1.404 + 23.54 + 1266.18 + 4.032 + 11.03 + 2.12 + 29.51 + 19.9 + 0.11 + 0.592

+ 0.91 =1417.328

DALY is 1417.328 or 68.25 DALY per 100 000 population

DALYfemales = 724.25

DALYmales = 693.07

The value of productivity losses is 472 751 172 denars or 7 687 011 € or 8 601 106 USD

DALY x GDP = 1417.328 x 333,551 denars = 472,751,172 denars

The gross domestic product in the Republic of North Macedonia for 2019 is 689 425 000 000 denars, of which the agriculture, forestry and fishing sector (gross domestic product according to the production method) is 55 477 000 000 denars.

The value of productivity losses is 0.852% of the assets of the agriculture, forestry and fisheries sector.

Discussion

Our research reveals that unsafe food-related diseases impose a significant global health burden, to-

taling 1,417.328 Disability-Adjusted Life Years (DALYs), equivalent to 68.25 DALYs per 100,000 population. This figure surpasses the European region's burden, where EUR A reports 41 DALYs, EUR B (including the Republic of North Macedonia) 52 DALYs, and EUR C 49 DALYs per 100,000 population[17].

Globally, a 2010 study on unsafe food-related illnesses estimated 600,652,361 cases, resulting in 418,608 deaths. These diseases accounted for 32,841,428 DALYs, including 5,589,028 Years Lived with Disability (YLDs) and 27,201,701 Years of Life Lost (YLLs)17. Regionally, the burden varies significantly:

- Eastern Mediterranean: EMR B at 362 DALYs and EMR D at 571 DALYs per 100,000 population.
- North America: AMR A at 35 DALYs, AMR B at 140 DALYs, and AMR D at 315 DALYs per 100,000 population.
- Western Pacific: WPR A at 36 DALYs and WPR B at 293 DALYs per 100,000 population.
- South-East Asia: SEAR B at 685 DALYs and SEAR D at 711 DALYs per 100,000 population.
- These findings underscore the urgent need for targeted interventions to address the disproportionate impact of unsafe food across regions.

A 2010 study on the global burden of unsafe food-related diseases found that diarrheal disease agents caused 548,595,679 cases worldwide, resulting in 230,111 deaths. These agents contributed to 17,659,226 Disability-Adjusted Life Years (DALYs), including 839,463 Years Lived with Disability (YLDs) and 16,821,418 Years of Life Lost (YLLs).

Regionally, the burden of diarrheal diseases varied significantly:

- South-East Asia: SEAR B at 330 DALYs and SEAR D at 380 DALYs per 100,000 population.
- Eastern Mediterranean: EMR B at 277 DALYs and EMR D at 393 DALYs per 100,000 population.
- North America: AMR A at 23 DALYs, AMR B at 60 DALYs, and AMR D at 72 DALYs per 100,000 population.
- Western Pacific: WPR A at 23 DALYs and WPR B at 41 DALYs per 100,000 population.
- Europe: EUR A at 28 DALYs, EUR B (including the Republic of North Macedonia) at 25 DALYs, and EUR C at 24 DALYs per 100,000 population.

The study also estimated that 31 hazardous agents in unsafe food caused a total of 33 million DALYs in 2010, comparable to major infectious diseases like HIV/AIDS (92 million DALYs), malaria (55 million DALYs), and tuberculosis (44 million DALYs). This burden is also similar to other risk factors, including poor diet (254 million DALYs), inadequate water and sanitation (211 million DALYs), and air pollution (76 million DALYs)[18]. These findings highlight the critical public health challenge posed by unsafe food and the need for robust global interventions.

Our study estimates productivity losses from unsafe food-related diseases at 472,751,172 MKD (7,687,011

EUR or 8,601,106 USD). Comparative studies highlight the global economic burden of foodborne illnesses:

- New Zealand (2010): Total costs reached 161.9 million NZD, including 16.4 million NZD in government costs, 12.3 million NZD in industry costs, and 133.2 million NZD in disease-related costs (treatment, lost output, and lifestyle impacts)19.
- Australia (2019): Foodborne illnesses cost 2.44 billion AUD annually (90% uncertainty interval: 1.65–3.68 billion), with Campylobacter, non-typhoidal Salmonella, Shiga toxin-producing E. coli, and norovirus as leading contributors[20].
- Denmark (2019): Seven food-related diseases generated a burden of 434 million EUR[21].
- United States (2015): Foodborne pathogens imposed a 15.5 billion USD economic burden annually, with five pathogens accounting for 90% of the costs[22].

These findings underscore the substantial economic impact of unsafe food across diverse economies, highlighting the need for targeted prevention and control measures.

- The first-ever estimates of foodborne diseases in the Republic of North Macedonia reveal a significant public health burden. The ranking of diseases, deaths, and Disability-Adjusted Life Years (DALYs) per hazard varies widely, with diarrheal disease agents identified as the primary contributors to illness. Notably, hazards causing the most cases do not always rank highest in deaths or DALYs. This discrepancy indicates that high-case-count diseases draw greater public health attention, while less frequent but severe diseases impose a substantial, often underrecognized burden. Factors such as symptom severity, duration, case fatality ratio, and age at death reshape the understanding of foodborne illnesses and highlight the need to prioritize both prevalent and severe hazards in public health strategies.[18]

Conclusion

A comprehensive understanding of the true burden of foodborne disease is crucial for developing evidence-based food safety policies and making informed decisions. Disability Adjusted Life Years (DALY) estimates provide a clear illustration of the impact of foodborne diseases in the European Region, enabling comparisons across different diseases and their effects on the population. This approach is essential for prioritizing food safety management efforts and formulating targeted policies to address foodborne diseases.

The Foodborne Disease Burden Epidemiology Reference Group (FERG) estimates offer a valuable resource, encouraging and guiding countries to conduct their own studies on the burden of foodborne disease. The World Health Organization (WHO) has provided tools to facilitate these studies, allowing countries to analyze the disease burden associated with food contamination and to describe the epidemiology of foodborne illness. These studies promote the

use of evidence-based information in food safety policy and decision-making, including setting priorities, enhancing risk communication, and raising food safety awareness. Ultimately, this approach helps prevent foodborne illness at both national and regional levels, improving public health and economic outcomes.

References

1. World Health Organization. WHO consultation to develop a strategy to estimate the global burden of foodborne diseases. Geneva: World Health Organization; 2006. p. vii. Available from: http://www.who.int/foodsafety/publications/foodborne_disease/fbd_2006.pd

2. Mathers CD. History of global burden of disease assessment at the World Health Organization. Arch Public Health. 2020 Aug 24;78:77. doi: 10.1186/s13690-020-00458-3.

3. Havelaar AH, Van Duynhoven YT, Nauta MJ, Bouwknegt M, Heuvelink AE, De Wit GA, Nieuwenhuizen MG, van de Kar NC. Disease burden in The Netherlands due to infections with Shiga toxin-producing Escherichia coli O157. Epidemiol Infect. 2004 Jun;132(3):467-84. doi: 10.1017/s0950268804001979.

4. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ. 2003;81(3):197-204. Epub 2003 May 16. PMID: 12764516.

5. Ssemanda JN, Reij MW, Bagabe MC, Muvunyi CM, Nyamusore J, Joosten H, Zwietering MH: Estimates of the burden of illnesses related to foodborne pathogens as from the syndromic surveillance data of 2013 in Rwanda. Microb Risk Anal 2018, 9:55-63 DOI: 210.1016/j.mran.2018.02.002

6. Etienne CF. Supplement on Caribbean burden of illness study. Foreword. J Health Popul Nutr. 2013 Dec;31(4 Suppl 1):1-2. PMID: 24992807.

7. Pires SM, Desta BN, Mughini-Gras L, Mmbaga BT, Fayemi OE, Salvador EM, Gobena T, Majowicz SE, Hald T, Hoejskov PS, Minato Y, Devleesschauwer B. Burden of foodborne diseases: think global, act local. Curr Opin Food Sci. 2021 Jun;39:152-159. doi: 10.1016/j.cofs.2021.01.006.

8. Lake RJ, Devleesschauwer B, Nasinyama G, Havelaar AH, Kuchenmüller T, Haagsma JA, Jensen HH, Jessani N, Maertens de Noordhout C, Angulo FJ, Ehiri JE, Molla L, Agaba F, Aungkulanon S, Kumagai Y, Speybroeck N. National Studies as a Component of the World Health Organization Initiative to Estimate the Global and Regional Burden of Foodborne Disease. PLoS One. 2015;10(12):e0140319. doi: 10.1371/journal.pone.0140319.

9. Institute for Health Metrics and Evaluation. Country Profiles. 2013. Available: http://www.healthdata.org/results/country-profiles.

10. World Health Organization. Food safety data by WHO region, 2018. Available: http://apps.who.int/gho/data/view.main.IHRREG11v?lang= en

11. World Health Organization. Estimating the burden of foodborne diseases: a practical handbook for

countries: a guide for planning, implementing and reporting country-level burden of foodborne disease. World Health Organization; 2021

12. Codex Alimentarius Commission. Principles and guidelines for the conduct of microbiological risk management. CAC/GL 63–2007. Available: www.codexalimentarius.org/input/download/standards/10741/ CXG_063e.pdf.
13. WHO: Workshop Report: National Workshop on Foodborne Disease Surveillance and Response; Hai Phong, Vietnam, 9-11 August 2016: 2016.
14. Flint JA, Van Duynhoven YT, Angulo FJ, DeLong SM, Braun P, Kirk M, et al. Estimating the burden of acute gastroenteritis, foodborne disease, and pathogens commonly transmitted by food: an international review. Clin Infect Dis. 2005; 41(5):698-704. doi: 10.1086/432064.
15. Pogreba-Brown K, Austhof E, Armstrong A, Schaefer K, Villa Zapata L, McClelland DJ, et al. Chronic gastrointestinal and joint-related sequelae associated with common foodborne illnesses: A scoping review. Foodborne Pathog Dis. 2020;17(2):67-86. doi: 10.1089/fpd.2019.2692.
16. Liu J, Luo B, Zhou Y, Ma X, Liang J, Sang X, et al. Prevalence and distribution of acute gastrointestinal illness in the community of China: a population-based face-to-face survey, 2014-2015. BMC Public Health. 2023;23(1):836. doi: 10.1186/s12889-023-15337-z.
17. World Health Organization. WHO estimates of the global burden of foodborne diseases: foodborne disease burden epidemiology reference group 2007-2015. World Health Organization; 2015
18. World Health Organization, The Burden of foodborne diseases in the WHO European region, WHO; 2017
19. Gadiel D, Abelson P. The economic cost of foodborne disease in New Zealand 2010, Prepared for New Zealand Food Safety Authority, AIE, available at: https://www.mpi.govt.nz/dmsdocument/25814-The-economic-cost-of-foodborne-disease-in-New-Zealand
20. Glass K, McLure A, Bourke S, Cribb DM, Kirk MD, March J, et al. The cost of foodborne illness and its sequelae in Australia Circa 2019. Foodborne Pathog Dis. 2023;20(10):419-426. doi: 10.1089/fpd.2023.0015.
21. Pires SM, Jensen JD, Jakobsen L, Ethelberg S, Christensen T. Health and economic burden of seven foodborne diseases in Denmark, 2019. Foodborne Pathog Dis. 2022;19(9):581-589. doi: 10.1089/fpd.2022.0031.
22. Hoffmann S, Maculloch B, Batz M, Economic burden of major foodborne illnesses acquired in the United States, Economic Information Bulletin No. (EIB-140) 59 pp, Department of Agriculture, Economic Research Service, May 2015 DOI: 10.22004/ag.econ.205081

PUBLIC HEALTH

OPINIONS AND ATTITUDES OF PARENTS AND HEALTHCARE WORKERS ON HEALTH EDUCATION AND IMMUNIZATION IN TUTIN MUNICIPALITY

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Abstract

Introduction: Negative attitudes and anti-vaccination propaganda are imposed daily on confused parents. In such a context, enhanced health education can play an important role in correctly understanding the role of vaccination in preserving health and changing people's behavior in that direction. The aim of this study was to explore whether the role of health education is adequately addressed within the healthcare system and the wider community. Materials and Methods: A qualitative study was conducted using the COM-B model to assess capability, opportunity, and motivation as three key factors for behavior change. The number of focus groups and number of participants were formed according the international and scientific rules. We conducted a total of 2 focus groups: with parents and with healthcare workers. All invited participants attended. The meetings were held in person, face-to-face, at the Health education Office of the Health Center Tutin between April 1 and May 30, 2024.Discussion topics included the experiences of healthcare workers in implementing immunization, identifying obstacles they face, suggestions for overcoming these obstacles, and for parents, the way they obtain information about vaccines, reasons for refusal, and the possibility of collaboration with healthcare workers and other social structures. Results: According to data from the Institute of Public Health of Serbia, in 2022, the municipality of Tutin had the worst coverage for the first revaccination of the DTaP-IPV-Hib vaccine - only 28.7%.The analysis covered focus groups with a total of 16 participants (9 parents and 7 healthcare workers). Among the parents, 44% were male, and 56% were female, with an average age of 33 years, while among healthcare workers, 29% were male, and 71% were female, with an average age of 41 years. Parents emphasized the need for clearer and verified information about vaccine safety, with 67% obtaining information from social media. Healthcare workers highlighted the importance of intensifying health education through schools and media, as well as the need for intersectoral collaboration. They also noted facing a lack of time and administrative barriers that limit the possibility of individualized approaches to parents. Conclusion: Parents and healthcare workers from Tutin municipality agree on the need for health education and that its planning and implementation in healthcare institutions, schools, and other collectives would contribute to a better understanding and easier decision-making regarding vaccination. Discussions with immunization providers and parents helped us understand their perspectives on the role of health education in improving the vaccination process.

ЈАВНО ЗДРАВЈЕ

МИСЛЕЊА И СТАВОВИ НА РОДИТЕЛИ И ЗДРАВСТВЕНИ РАБОТНИЦИ ЗА ЗДРАВСТВЕНАТА ЕДУКАЦИЈА И ИМУНИЗАЦИЈАТА ВО ОПШТИНА ТУТИН

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Клучни зборови: имунизација, здравствено образование, здравствени работници, родители, фокус група, Тутин

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Печатарски права: ©2025. Митхат Еминовиќ, Селма Хабибовиќ. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа ториганалниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Вовед: Негативните ставови и пропагандата против вакцинацијата секојдневно им се наметнуваат на збунетите родители. Во таква констелација, засилената здравствена едукација може да одигра важна улога во правилното разбирање на улогата на вакцинацијата во зачувување на здравјето и промената на однесувањето на луѓето во таа насока. Цел на оваа студија беше да се истражи дали улогата на здравствената едукација има адекватен третман во здравствениот систем и пошироко во заедницата. Материјал и методи: Се спроведе квалитативна студија, користејќи го COM-B моделот за проценка на способноста, можноста и мотивираноста, како три клучни фактори за промени во однесувањето, како и според меѓународните и научни правила за формирање на потребен број на фокус групи и број на учесници во фокус групите. Спроведовме интервју со вкупно 2 фокус групи: со родители и со здравствени работници. Присуствуваа сите поканети учесници. Состаноците се одржаа лично, лице в лице, во Канцеларијата за здравствена едукација на Здравствениот дом Тутин помеѓу 1 април и 30 мај 2024 година.Темите на разговор беа искуствата на здравствените работници во спроведувањето на имунизацијата, дефинирањето на пречките на кои наидуваат, предлози за нивно надминување, а кај родителите начинот на информирање за вакцините, причините за нивно одбивање, како и можноста за соработка со здравствените работници и други општествени структури. Резултати: Според податоците на Институтот за јавно здравје на Србија, во 2022 година, општина Тутин имала најлоша покриеност за првата ревакцинација на вакцината DTaP-IPV-Hib - само 28,7%. Анализата опфати фокус групи со вкупно 16 учесници (9 родители и 7 здравствени работници). Кај родителите 44% беа од машки, а 56% од женски пол, со просечна возраст од 33 години, додека кај здравствените работници 29% беа од машки, а 71% од женски пол, со просечна возраст од 41 година. Родителите истакнаа потреба од појасни и потврдени информации за безбедноста на вакцините, при што 67%, добивале информации од социјалните мрежи. Здравствените работници укажаа на важноста од интензивирање на здравствената едукација преку училишта и медиуми, како и потребата од меѓусекторска соработка. Тие нагласија дека се соочуваат со недостаток на време и административни пречки кои ја ограничуваат можноста за индивидуален пристап кон родителите. Заклучок: Родителите и здравствените работници од општина Тутин се согласуваат дека е потребна здравствена едукација и дека нејзиното планирање и спроведување во здравствените установи, училиштата и другите колективи би придонело за подобро разбирање и полесно донесување одлуки за вакцинација. Разговорите со изведувачите на имунизацијата и родителите ни помогнаа да ги согледаме ставовите за улогата на здравствената едукациј во подобрата реализација на вакцинацијата.

Introduction

Planned and high-quality health education work can significantly influence changes in people's behavior and attitudes toward public health activities, particularly immunization. Immunization is a groundbreaking scientific and civilizational achievement. The World Health Organization has ranked it second in importance for preserving human health, immediately after the provision of safe water. Thanks to the successful implementation of immunization, millions of lives have been saved[1]. However, vaccination coverage has been declining year after year. Many parents, influenced by the propaganda of individuals and groups against vaccination, refuse to vaccinate their children[2].

The reasons cited for refusing to vaccinate their children lack scientific basis. With quality and well-planned health education, these reasons can largely be refuted, helping parents change their attitudes and beliefs to vaccinate their children. To achieve this, communication and collaboration with parents must be established, experts must be present in the media, lectures by experts organized, and promotional materials published.

There are many factors that influence the formation of incorrect and harmful attitudes and beliefs about vaccines. Therefore, it is essential to investigate the impact of health education on changing these beliefs. The COM-B (Communication, Opportunities, Motivation – Behaviour) model is suitable for assessing this impact. Difficulties arise when quantifying the influence of health education on changing attitudes toward vaccination, which presents a challenge for future work in this field. It is possible to evaluate the impact of any activity aimed at increasing vaccination coverage by measuring the number of people vaccinated or those who refuse vaccination. However, the role of health education is to enable the population to form correct attitudes and beliefs based on scientific evidence. This process is complex, extends over a long period, and encompasses a broader population.

The ability to measure the outcomes of these processes, such as attitudes toward vaccination, complicates the assessment of where health education has a decisive influence on the decision to vaccinate and where it does not3,4.

To identify points and methods of intervention through health education methods, we conducted a qualitative study of two focus groups directly involved in the immunization process. Particularly significant were the attitudes and suggestions of the parent focus group, as their decisions directly determine the percentage of vaccination coverage.

This study aimed to help us understand the experiences and thoughts of healthcare workers and parents regarding the potential for health education to influence behavior and attitudes toward the immunization process.

Materials and Methods

For the purposes of conducting this qualitative study, we used the COM-B model to assess capability, opportunity, and motivation as three key factors for behavior change. We formed two focus groups:

1. Parents or guardians of children who were either not vaccinated at all or partially vaccinated.
2. Healthcare workers involved in the immunization process (planning, execution, and evaluation).

To select participants for the focus groups, we used a practical and stratified sampling method5. Two focus groups were conducted with parents and healthcare workers.

The parent focus group was composed of parents or guardians of children who were either not vaccinated at all or only partially vaccinated, while the healthcare worker focus group included individuals directly involved in the immunization process.

Potential participants were contacted via telephone to verify if they met the criteria, and arrangements were made for the time and place of the focus group meetings. At the beginning of the discussion, the purpose of the study was explained, and participants filled out and signed a form with basic information. Each session lasted between 40 and 60 minutes.

During the discussion, parents presented their experiences, attitudes, and beliefs. They were asked to share their thoughts on the need for health education, improved communication with healthcare workers, and whether educational and other institutions should be involved in the entire process. The discussion was encouraged to develop and foster an exchange of experiences. Participants were also asked to express their opinions on the need to clarify the effects of immunization and possible adverse reactions.

A discussion with healthcare workers was focused on the barriers they identified in implementing immunization. They were invited to share their experiences and thoughts on activities that could potentially increase vaccination coverage and how health education might influence this.

All invited participants attended. The meetings were held in person, face-to-face, at the Health education Office of the Health Center Tutin between April 1 and May 30, 2024.

The inclusion criteria for study participants included:

- Parents with children under the age of 7 who have decided not to vaccinate them or have partially vaccinated them.
- Healthcare workers who are actively involved in the immunization process (doctors, nurses).
- The ability to participate in focus groups and express opinions on vaccination.

Exclusion criteria:

- Parents who have already fully vaccinated their children.
- Healthcare workers with no experience in immunization.
- Individuals who have previously participated in similar studies to avoid bias.

Results

The total of 9 parents participated in focus group. Their age ranged from 29 to 37 years, five were women, and four were men, all with completed secondary education. Most of them were acquainted with one another.

From healthcare workers directly involved in the immunization process, we formed group with a total of seven participants (three pediatricians and four nurses).

Table 1: Characteristics of the Focus Groups:

Focus Group	Number of Participants	Gender (% Male/ Female)	Age (Average)	Education	Key Discussion Topics
Parents/ Guardians	9	44%/56%	33 years	Secondary education	Fears, sources of information, trust in the healthcare system
Healthcare Workers	7	29%/71%	41 years	Higher/ secondary education	Barriers to vaccination promotion, strategies to increase coverage

A) Key insights and results of discussions with parents are presented below.

Concerns and Fear of Vaccines

Our question was: what causes concern among parents, and why is there distrust in vaccines? The answers and perspectives varied. Some parents expressed a lack of trust in the vaccine's effectiveness, doubting its quality. One parent mentioned believing that natural immunity against infectious diseases is better ("Our parents didn't receive vaccines and were healthy"). Another mother shared an unpleasant experience during the administration of the first vaccine dose: *"My baby's thigh swelled up and was very painful. My baby cried nonstop for two hours. After that, I decided not to take them for the second dose."*

Despite their expressed doubt and mistrust, the parents were open to the conversation and listened to other opinions and perspectives. None of them denied the benefits of vaccines or rejected the possibility of starting or continuing the immunization of their children. The primary factor influencing their decision not to vaccinate was fear of potential consequences and side effects: *"I will vaccinate my child if I am convinced that there will be no negative effects on their health."*

Sources of Information About Vaccines

When asked about how they obtain information about vaccines, the responses varied. However, a common theme among all parents was that they did not receive sufficient information from healthcare workers. In their search for the "truth about vaccines," they turned to social media, listening to experiences and opinions shared by acquaintances who claimed that *"vaccines are harmful and part of a larger conspiracy."*

Some parents also mentioned receiving inconsistent advice from healthcare workers: *"One doctor told me to vaccinate my child with the MMR vaccine only after they start walking and talking."*

All parents agreed on the importance of having access to accurate information from experts,and the space to address their doubts and fears. They felt that they were not given enough attention and that the advantages of vaccination compared to the consequences of preventable diseases were not convincingly explained to them: *"The doctor told me they didn't have time for my questions and that I should read the vaccine instructions and decide on my own whether to vaccinate my child or not."*

Parents who had such experiences and sought additional information were more susceptible to disinformation and propaganda from anti-vaccination groups.

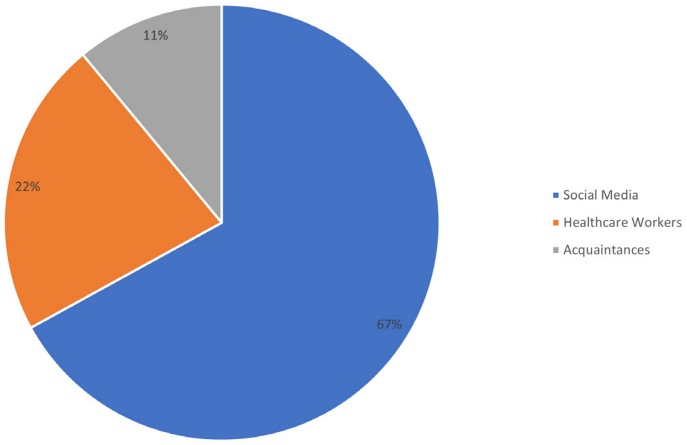


Chart 1: Sources of Information

The Role of Trust in Decision-Making

Parents reported that trust in healthcare workers, as well as their recommendations and advice, plays a crucial role in their decision-making process regarding whether to vaccinate their child. Patient and well-reasoned explanations of the benefits of vaccination in protecting their child's health, provided by knowledgeable professionals, would contribute to making the right decision. Long-term relationships and positive experiences with healthcare workers in delivering other health services also strengthen this trust: *"This doctor treated my other children, and I know she wouldn't recommend something unless she was sure it was good for my child."*

However, this trust can easily be lost if the healthcare worker does not show patience, especially if they do not insist on vaccination, leaving parents uncertain and confused. In such situations, parents often succumb to the influence of anti-vaccination advocates, who exhibit remarkable aggression in discouraging parents from vaccination, using various conspiracy theories and exaggerating or misrepresenting adverse events as "evidence."

The only "arguments" presented by anti-vaccination advocates are anecdotal experiences that are often misinterpreted and distorted: *"A friend told me she knows a woman whose child showed symptoms of autism immediately after receiving the MMR vaccine."*

Long-Term Benefits of Health Education

Health education encompasses numerous methods and forms that, thanks to advancements in communication tools, are accessible to a broad population. Discussions within the focus groups also include elements of education, knowledge exchange, and experience sharing. However, it is particularly important for participants to continue discussions and reflections on vaccination after the session, engaging with family members, friends, colleagues, and others.

The new insights gained during the meetings, and subsequent discussions about vaccination, encourage parents to rethink their attitudes and beliefs. By considering all the benefits of protecting their children with vaccines and the dangers of diseases for unvaccinated children, parents often reevaluate their decisions:

"I didn't know that measles could cause such serious complications and that the vaccine can prevent this without being harmful."

B) During the sessions with healthcare workers, all aspects of the immunization process were discussed, from planning to implementation and evaluation. They shared their experiences and reflected on ways to increase vaccination coverage among the population. They emphasized that health education is particularly significant for restoring trust in the healthcare system and for changing the attitudes and beliefs of those opposed to vaccination.

Collaboration with Parents is Crucial

Healthcare workers involved in the immunization process emphasize the need to identify issues in their relationship with parents and to find appropriate solutions. All agree that health education is highly important and should be planned and implemented at multiple levels, not just within the healthcare system. Schools and educators play a significant role in this process.

It has been observed that parents need more information about vaccines themselves, as well as potential health consequences for their children. Concerned about their children's health, parents often overlook the significant benefits of vaccination:

"One parent, while rejecting vaccination for their child, persistently recounted negative experiences of 'some' parents during vaccination, describing alleged discomfort and illnesses that occurred. When I pointed out that such claims have been disproven by numerous scientific studies, they had no response."

In addition to helping parents make the right decision, it is essential to show understanding for their concerns and to support their need for additional information and consultations with trusted experts.

Mutual Collaboration and Coordination

Healthcare workers have differing opinions on how and when to assist parents in making the decision to vaccinate their children. Some believe the pediatrician's office is the right time and place, while others think health education methods

should be employed through other healthcare system services (e.g., home care services, home visits), as well as through other institutions (e.g., schools, kindergartens, media, lectures, roundtables, NGOs, etc.).

Healthcare workers need to communicate more effectively among themselves and coordinate their vaccination promotion activities. This would strengthen the confidence of healthcare workers and reduce the potential for confusing parents:

"When I recommended that a child should receive the prescribed vaccines, one mother told me her doctor had not given her such advice," shared a nurse.

In addition to patience and understanding toward parents, healthcare workers must contribute to strengthening their authority and trustworthiness. Most healthcare workers agree that good communication—with parents and among themselves—builds and maintains trust.

Barriers to Implementing Health Education

All healthcare workers are aware of the importance of health education, but they emphasize the challenges and obstacles in its planning, implementation, and especially in analyzing its effects on vaccination decision-making. The most frequently mentioned reasons for insufficient engagement in the health education process are a lack of time, being overburdened with providing other services, and excessive administrative tasks.

For parents to develop trust and listen to the recommendations and advice of healthcare workers, the latter must demonstrate patience and persistence. One doctor noted:

"While adhering to all administrative procedures, I have very little time left for examinations, let alone for individual health education efforts."

Another highlighted:"Sometimes, due to a lack of time, we give parents too much information without thoroughly explaining it, leaving them overwhelmed and even more confused."

Schools and other social institutions, which could play a role in the education process, are not involved. This creates an opportunity for anti-vaccination advocates to influence concerned and confused parents through social media and other means.

Table 2: Key Barriers and Solutions in Promoting Vaccination

Focus Group	Barriers	Solutions
Parents	• Doubts about vaccine quality • Fear of side effects • Distrust in the healthcare system • Lack of information	• Health education • Restoring trust in the healthcare system • Improved communication with healthcare workers • Reliable information
Healthcare Workers	• Lack of time and excessive administrative tasks • Poor communication with parents • Anti-vaccination campaigns • Lack of engagement from other services and institutions	• Health education • Better communication • Strengthening authority • Involvement of schools and media

Discussion

Through this research involving focus groups of parents and healthcare workers, discussions were conducted to explore the potential of health education in improving vaccination coverage among the population.

We spoke with parents and those directly involved in the immunization process to understand their experiences, fears, and thoughts on improving the situation. Parents expressed concerns about their children's health and highlighted the need for accurate information about vaccines and their effects to make decisions that would benefit their children. Their dilemmas often stem from the spread of misinformation by anti-vaccination advocates. Comprehensive and high-quality health education could restore trust in the healthcare system, help parents resolve their doubts, and protect their children from infectious diseases. This would ultimately improve vaccination coverage and achieve herd immunity, which acts as a barrier against outbreaks.

There have been many examples of outbreaks caused by a decline in vaccination coverage, such as the measles outbreak in Serbia in 2018, where approximately 6,000 people were infected, and 15 died[6].

Parents considered various arguments when making decisions about vaccination. They also displayed differing preferences for how information was presented and the methods of health education. Some preferred group discussions, while others favored individual approaches. Similar findings have been observed in other qualitative studies on communication preferences[7].

Healthcare workers' thoughts and experiences were generally aligned, agreeing on the necessary steps to improve vaccination coverage through health education. They exhibited a high degree of self-criticism and readiness to put more effort into all phases of the immunization process.

Comparing the responses from the focus group discussions, both parents and healthcare workers agreed on the necessity of health education and that its planning and implementation in healthcare facilities, schools, and other institutions would contribute to better understanding and easier decision-making about vaccination.

Successful implementation of health education and effective communication between parents and healthcare workers involved in immunization could significantly increase the participation of hesitant parents, thereby improving vaccination coverage. The information provided by healthcare workers is often insufficient to convince parents of the undeniable benefits of vaccines.

The perception of responsibility for the lack of health education and evidence-based promotion of vaccination differs between parents and healthcare workers. Healthcare workers, as direct participants in the immunization process, acknowledge some responsibility and demonstrate a degree of self-criticism. They express a willingness to participate in creating and implementing activities in health education involving all societal structures.

Parents, on the other hand, rarely display a critical stance regarding their own knowledge about vac-

cines or the beliefs they have formed based on uncertain and unscientific information.

Healthcare workers understand parents' concerns and criticisms, support intensive health education, and emphasize the need to adapt the healthcare system, promote public health concepts, and involve all societal factors, particularly the educational sector. Health education, through the promotion of immunization, could influence changes in parental behavior[8,9].

The knowledge level of healthcare workers involved in the immunization process is crucial, confirming the importance of direct communication between immunization providers and parents to make the right decision[10,11].

There are few studies that have analyzed the issue of immunization and health education as a tool for achieving better vaccination coverage in this way. One challenge in preparing this study was organizing discussions about the impact of health education on the immunization process with a focus group of parents who lacked sufficient knowledge or experience with vaccination. Researchers in similar studies have faced this issue as well[12].

In this study, we analyzed only the content of the focus group discussions without attempting to classify participants' responses. As the saying goes, "*If something is not classified, it cannot be measured*"[13]. This represents a minor limitation of the study.

On the other hand, participants were free to speak about their beliefs and attitudes in the way they think and understand. This is an advantage of the study, as is the composition of the focus group, including direct participants in the immunization process, whose experiences and thoughts are authentic and critical for analysis and conclusions.

The results of this study highlight key issues in the immunization process and parental perceptions. However, they should be interpreted in the context of methodological limitations. While focus groups allow for a deeper understanding of attitudes, future studies should include a larger number of participants and apply more rigorous sampling methods. Despite these limitations, our findings indicate that parents are interested in obtaining additional information about vaccination and that there is a need to improve communication between healthcare workers and parents.

Study Limitations

Although this study provides valuable insights into the attitudes of parents and healthcare workers toward immunization, several limitations should be considered:

- Sample size: The study was conducted on a small number of participants (16 in total), which may affect the generalizability of the results. A larger and more representative study could provide more reliable data.
- Sampling method: Although the sample was stratified and practical, future studies should employ random sampling to reduce the potential for bias.
- Subjective nature of responses:

The qualitative analysis is based on participants' statements, which may include personal perceptions and experiences that cannot always be generalized.

Conclusion

This study provides an insight into different opinions regarding the emergence and resolution of issues in the vaccination process through the analysis of focus group discussions. Regular communication, along with planned and high-quality health education for the population, can significantly contribute to understanding the importance and benefits of immunization, as well as the risks faced by unprotected individuals.

Healthcare workers directly involved in the immunization process bear a particular responsibility to address parents' fears and concerns through effective communication and accessible health education methods, helping them make informed decisions.

The immunization process, as a topic of health education, should also be a responsibility of other institutions and societal actors, not just the healthcare system.

The problems and solutions identified by the participants in this study can serve as a foundation for further research, especially for attempts to classify and quantify responses[14]. This would enhance the evaluation of the impact of health education on behavioral changes regarding vaccination.

References

1. Radovanović Z. *Istina o vakcinama*. Smederevo: 2016. pp. 11-17.
2. Bedford H, Attwell K, Danchin M, Marshall H, Corben P, Leask J. Vaccine hesitancy, refusal and access barriers: The need for clarity in terminology. *Vaccine*. 2017; 35(36): 4473-4479. doi:10.1016/j.vaccine.2017.06.008.
3. Pigott T, Shepperd S. Identifying, documenting, and examining heterogeneity in systematic reviews of complex interventions. *J ClinEpidemiol*. 2013; 66(11): 1244-1250. doi:10.1016/j.jclinepi.2013.06.001.
4. WHO SAGE Working Group on Vaccine Hesitancy. Report of the SAGE Working Group on Vaccine Hesitancy. Geneva: World Health Organization; 2014. Available from: WHO Website. Accessed: 23.08.2024.
5. Patton MQ. Designing qualitative studies. In: *Qualitative evaluation and research methods*. Beverly Hills, CA: SAGE Publications; 1990. p. 169-186.
6. InstitutzajavnozdravljeSrbije "Dr Milan Jovanović Batut". Aktueln aepidemiološkasituacijamalihbo ginja (morbila) u RepubliciSrbiji. Available from: Batut Website. Accessed: 23.08.2024.
7. Ames H, Glenton C, Lewin S. Parents' and informal caregivers' views and experiences of communication about routine childhood vaccination: a synthesis of qualitative evidence. *Cochrane Database Syst Rev*. 2017; (2): CD011787. doi:10.1002/14651858.CD011787.pub2.

8. Koh HK, Rudd RE. The arc of health literacy. *JAMA*. 2015; 314(12): 1225-1226. doi:10.1001/jama.2015.9792.

9. Hill S, Lowe D, Liu C, Santesso N. Building health-literate societies. In: Hill S, editor. *The Knowledgeable Patient: Communication and Participation in Health*. Chichester: Wiley Blackwell; 2011. p. 184-195.

10. Legare F, Thompson-Leduc P. Twelve myths about shared decision making. *Patient EducCouns*. 2014; 96(3): 281-286. doi:10.1016/j.pec.2014.06.014.

11. Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient EducCouns*. 2006; 60(3): 301-312. doi:10.1016/j.pec.2005.06.010.

12. Keeley T, Williamson P, Callery P, Jones LL, Mathers J, Jones J, et al. The use of qualitative methods to inform Delphi surveys in core outcome set development. *Trials*. 2016; 17: 230. doi:10.1186/s13063-016-1320-3.

13. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ*. 1995; 311(6996): 425-429. doi:10.1136/bmj.311.6996.425.

14. Kaufman J, Ryan R, Glenton C, Lewin S, Bosch-Capblanch X, Cartier Y, et al. Childhood vaccination communication outcomes unpacked and organized in a taxonomy to facilitate core outcome establishment. *J ClinEpidemiol*. 2017; 84: 173-184. doi:10.1016/j.jclinepi.2017.02.012.

CLINICAL SCIENCE

MEASURING THE EFFICACY OF TREATMENT WITH NEUROFEEDBACK METHOD IN PATIENTS WITH AFFECTIVE DISORDERS

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Abstract

Depression affects approximately 280 million people globally, with about 5% of adults experiencing an episode each year, making it a major public health concern. The high prevalence of treatment-resistant depression and the limitations of standard therapies highlight an urgent need for alternative treatments, such as neurofeedback, which has shown promising results in improving depressive symptoms when used alongside conventional pharmacological approaches. Aim of the study: To assess the efficacy of combining neurofeedback training with standard antidepressant therapy in adult patients with affective disorders. Materials and methods: This prospective, randomized study was conducted at the University Clinic for Psychiatry in Skopje, in a 2 month period. It involved a total of 100 outpatients diagnosed with affective disorders (ICD-10 codes F32, F33, F34). Participants were randomized into two groups: the study group (SG) that received both neurofeedback and antidepressant therapy, and the control group (CG) that received antidepressant monotherapy. The HAM-D and HAM-A scales, alongside with a structured psychiatric interview and sociodemographic questionnaire at baseline, were used to assess depressive and anxiety symptoms at baseline, 2 weeks, and 1 month. Data were analyzed with SPSS v23.0, using parametric and non-parametric tests, with significance set at $p<0.05$. The study received ethics approval, and all participants provided informed consent. Results: At baseline, both groups showed similar levels of depression and anxiety symptoms, with comparable average scores on the HAM-D (SG: 17.98 ± 5.7, CG: 18.42 ± 6.1) and HAMA (SG: 17.98 ± 6.8, CG: 21.36 ± 8.3) scales. At the two-week follow-up, the study group (SG) exhibited significant reductions in both HAM-D and HAMA scores compared to the control group (CG), with a decrease of 2.42 points in HAM-D (or 13.46% vs 0.65%) ($p<0.0001$) and 2.86 points in HAMA (13.72%, $p<0.0001$) for the SG, while the CG showed minimal change by 3.78%. At one-month follow-up, the SG continued to demonstrate marked improvement, with HAM-D scores at 14.50 ± 5.5 versus 17.56 ± 6.2 in the CG ($p=0.0064$) and HAMA scores at 16.82 ± 6.7 in the SG compared to 20.14 ± 8.3 in the CG. Conclusion: The results from the study suggest that neurofeedback, when combined with medication, may enhance both early and sustained symptom improvement of depression and anxiety.

КЛИНИЧКИ ИСТРАЖУВАЊА

МЕРЕЊЕ НА ЕФИКАСНОСТ НА МЕТОДАТА NEUROFEEDBACK ПРИ ТРЕТМАН НА ПАЦИЕНТИ СО АФЕКТИВНИ РАСТРОЈСТВА

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Печатарски права: ©2025 Александар Ристески, Славица Арсова, Елизабет Мицева-Величковска, Ана Филипче, Стефанија Митровска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Депресијата погодува приближно 280 милиони луѓе на глобално ниво, при што околу 5% од возрасните доживуваат епизода секоја година, што ја прави голем товар за јавното здравје. Високата преваленција на депресија резистентна на третман и ограничувањата на стандардните терапии ја нагласуваат итната потреба за алтернативни третмани, како што е неврофидбекот, кој покажува ветувачки резултати за подобрување на депресивните симптоми кога се користи заедно со конвенционалните фармаколошки пристапи. Цел на студијата: Да се процени ефикасноста на комбинирањето на неврофидбек тренинг со стандардна антидепресивна терапија кај возрасни пациенти. Материјали и методи: Оваа проспективна, рандомизирана студија беше спроведена на Универзитетската клиника за психијатрија во Скопје во текот на 2 месеци, во која беа вклучени 100 пациенти дијагностицирани со афективни растројства (МКБ-10 кодови F32, F33, F34). Учесниците беа поделени во две групи: испитувана група (ИГ) доби и неврофидбек и антидепресивна терапија, додека контролната група (КГ) беше лекувана со антидепресивна монотерапија Скалите HAMD и HAMA, заедно со структурирано психијатриско интервју и социодемографски прашалник, беа користени за проценка на симптомите на депресија и анксиозност на почетокот, 2 недели и 1 месец од почетокот на третманот. Податоците беа анализирани со SPSS v23.0, користејќи параметарски и непараметриски тестови, со статистичка значајност поставена на $p<0.05$. Студијата беше одобрена од етичката комисија и сите учесници дадоа информирана согласност за учество. Резултати: На почетокот, двете групи покажаа слични нивоа на симптоми на депресија и анксиозност, со споредливи просечни резултати на HAMD (ИГ: 17,98 ± 5,7, КГ: 18,42 ± 6,1) и HAMA (ИГ: 17,98 ± 6,8, КГ: 21. ± 8.3) скалите. На двонеделното следење, испитуваната група (ИГ) покажа значителни намалувања и во резултатите на HAMD и HAMA споредено со контролната група (КГ), со намалување од 2,42 поени во HAMD (или 13,46% наспроти 0,65%) ($p<0,0001$) и 2,86 поени во HAMA (13,72%, $p<0,0001$) за ИГ, додека КГ покажа минимална промена од 3,78%. До едномесечното следење, ИГ продолжи да демонстрира значително подобрување, со HAMD резултати од 14,50 ± 5,5 наспроти 17,56 ± 6,2 во КГ ($p=0,0064$) и HAMA резултати од 16,82 ± 6,7 во ИГ во споредба со 20,14 ± 8,3 во КГ. Заклучок: Резултатите од студијата сугерираат дека неврофидбек третманот комбиниран со лекови може да го забрза и одржи подобрувањето на депресивните и симптомите на анксиозност.

Introduction

Depression affects approximately 280 million individuals worldwide, representing a major global health issue that is often neglected despite its significant impact[1]. Each year, around 5% of adults experience an episode of depression, with prevalence rates varying across different regions and demographic groups[2]. The highest prevalence is observed in North America (4.4% for women and 2.5% for men) and the lowest in the Western Pacific[3]. Women are disproportionately affected, experiencing depression nearly twice as often as men, with hormonal changes during puberty, menstruation, pregnancy, and perimenopause, as well as different psychosocial stressors between genders, different learnt models of behavior and socio-economic inequities contributing to this disparity [4,5]. While retrospective reports suggest a 10.6% average lifetime prevalence, prospective studies estimate a higher range of 30-40%, underscoring the pervasive nature of the condition and the need for effective treatment strategies [3,6]. Moreover, depression is projected to be the leading cause of disease burden by 2030, particularly impacting women[1,7]. Furthermore, the risk factors associated with the COVID-19 pandemic such as greater exposure to stressors, lower social, healthcare and economic resources, employment loss, isolation and fear, contributed to a dramatic increase in the prevalence of depression worldwide reaching 25%, which is seven times higher than the pre pandemic estimates[4]. This alarming trend highlights the urgency for comprehensive research and interventions to mitigate its widespread consequences, which beyond significant subjective suffering, accompanying disability and high risk of suicide in affected individuals, contribute to broader social impacts and economic burden due to the high rates of recurrence and relapse[4,7].

In spite of evidence supporting the efficacy of conventional antidepressants, psychotherapeutic interventions, and additional modalities, the majority of individuals with major depressive disorder (MDD) show inadequate responsiveness to first-line treatments while a significant proportion fail multiple antidepressant interventions, leading to treatment-resistant depression (TRD). TRD is characterized by the inadequate response to conventional antidepressant treatments, despite adherence to appropriate dosage and duration. According to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), TRD is defined as the failure to respond to at least two different antidepressant regimens under these conditions[8,9]. This condition is significant as it affects approximately 30% of individuals with MDD, and accounting for nearly 50% of the total annual burden estimated $43.8 billion in recent studies from the U.S.[4,10,11]. The high prevalence and treatment challenges associated with TRD emphasizes the need for exploring alternative and adjunctive therapeutic options.

Neurofeedback training, a non-invasive intervention, has emerged as a promising supplementary treatment for major depressive disorder, showing significant improvements in depressive symptoms and neurophysiological outcomes, even in patients who do not achieve sufficient remission of symptoms with standard

pharmacological treatments[12,13]. Systematic reviews and meta-analyses support its potential efficacy as an adjunction in enhancing the outcomes of conventional therapies, underscoring its low risk of side effects and beneficial impact on neuropsychological function [12].

The aim of this study was to assess the efficacy of combining neurofeedback training with standard antidepressant therapy in adult patients with affective disorders, and to determine if this combined approach could enhance symptom reduction in comparison to antidepressant monotherapy.

Materials and methods

This prospective, randomized, controlled study was conducted at the University Clinic for Psychiatry, Skopje, North Macedonia, over the course of 2 months. The study aimed to evaluate the efficacy of combining neurofeedback training with standard antidepressant therapy in patients diagnosed with affective disorders. The study included 100 outpatients aged 18 to 65 years, diagnosed with affective disorders per ICD-10 codes F32 (depressive episode), F33 (recurrent depressive disorder), and F34 (persistent affective disorder). Participants were randomized into two groups of 50: the study group (SG) receiving combined antidepressant and neurofeedback treatment, and the control group (CG) treated solely with antidepressant as monotherapy. The SG received neurofeedback sessions in addition to antidepressants (SSRIs, SNRIs, NASsA). The neurofeedback utilized the "Encephalan-EEGR-19/26" device with "Rehacor" software for alpha/theta training, applied in 10 sessions of 25 minutes each. The CG was treated with monotherapy, including SSRIs (e.g., Escitalopram 10 mg), SNRIs (e.g., Duloxetine 60 mg), or NASsA (e.g., Mirtazapine 30 mg).

Participants in this study were assessed at three time points: baseline, 2 weeks, and 1 month after the start of treatment. Baseline data collection included a structured psychiatric interview, a sociodemographic questionnaire, and psychodiagnostic assessments using the HAMD and HAMA scales to measure affective symptoms. The HAMD and HAMA scales were also administered at the second (2 weeks) and third (1 month) assessment point to evaluate changes in depressive and anxiety symptoms over the course of the treatment.

The HAMD17 scale was utilized to assess depressive symptomatology, encompassing a range of clinical features associated with major depressive disorder, including affective symptoms, insomnia, hypochondriasis, and weight loss. The HAMD is a widely used clinician-rated scale for evaluating the severity of depression and treatment response in patients diagnosed with depressive disorders [14-18].

To compare the study and control groups regarding demographic and clinical characteristics and the total scores on the HAMA scale and HAMD scale, non-parametric tests (Pearson Chi-square and Fisher's exact test) and a parametric test (t-test for independent samples) were used. Testing the differences in the total scores on the HAMA scale and HAMD scale between the three assessment points (baseline, two weeks and 1 month

after treatment initiation) within the groups was performed using the parametric t-test for dependent samples. Statistical significance was defined at a level of $p<0.05$.

Results

Comparative analysis in terms of demographic and clinical characteristics Patients from both groups, study and control, were homogenous in terms of sex, and there was a statistically insignificant difference regarding sex (p=0.84). Female patients were predominant in both groups (52% and 54% in the study and in the control group, respectively) (Table 1).

Forty percent from the SG and 14% of patients from the CG were aged between 18 and 34 years; 30% from the SG and 22% from the CG were aged between 35 and 44 years; 26% from the SG and 60% from the CG were aged between 45 and 64 years; 4% from each group were 65 years of age or older (Table 1).

Table 1. Demographic distribution of patients

Sex	Groups			p-level
	n	SG n=50	CG n=50	
Male	47	24 (48%)	23 (46%)	X2=0.04
Female	53	26 (52%)	27 (54%)	p=0.84
Age	**n**	**SG** n=50	**CG n=50**	
18 – 34	27	20 (40%)	7 (14%)	X2=13.56
35 – 44	26	15 (30%)	11 (22%)	**p=0.0035
45 – 64	43	13 (26%)	30 (60%)	
≥65	4	2 (4%)	2 (4%)	

X^2 (Pearson Chi-square)

Comparative analysis by HAMA (Hamilton Anxiety Rating Scale)

Scores on the Hamilton Anxiety Rating Scale calculated for both groups at baseline and during the first follow up are given in Table 2.

Table 2. HAMA scale on baseline examination and first follow up assessment

HAMA 0 and HAMA 1		Groups		p-level
		SG n=50	CG n=50	
HAMA 0	mean ±SD	20.84 ± 7.0	22.20 ± 8.2	t=0.89
HAMA 0	min- max	8 – 41	6 – 46	p=0.375
HAMA 1	mean ±SD	17.98 ± 6.8	21.36 ± 8.3	t=2.23
HAMA 1	min- max	6 – 39	5 – 46	*p=0.028

t (Student t-test)

Quantitative analysis made by HAMA scores at baseline, that is, at the beginning of antidepressant treatment showed an average score of 20.84 ± 7.0 in the SG, and 22.20 ± 8.2 in the CG, with no statistically significant difference between the groups (p=0.375). In accordance with the

total HAMA result, at baseline both groups of patients most often suffered from mild to moderate anxiety (42% *vs.* 50%), followed by mild anxiety (34% *vs.* 22%). There was a statistically non-significant difference in the distribution of patients with mild, mild to moderate, moderate to severe and severe anxiety between patients from both groups (p=0.597).

The average HAMA score was 17.98 ± 6.8 in the SG, and 21.36 ± 8.3 in the CG on the first follow-up assessment, two weeks after treatment initiation. The difference of an average 3.38 scores was statistically significant (p=0.028). Patients treated with antidepressants in combination with neurofeedback (SG) showed a significantly lower score on the anxiety scale than patients treated with antidepressant medications alone (CG).

Table 3 illustrates the distribution of patients from both groups and the different severity of anxiety symptoms presented in number and percentage. During the first follow-up assessment, in accordance with the interpretation of the total HAMA score, mild anxiety was more often registered in patients from the study group compared to the control group (48% *vs.* 30), and mild to moderate anxiety was rarely encountered (36% *vs.* 44%), followed by moderate to severe anxiety (14% *vs.* 16%), and severe anxiety was rarely seen (2% *vs.* 10%, respectively). These differences between the groups were not statistically significant (p=0.16).

Table 3. Distribution of patients by HAMA categories at the first follow-up assessment

HAMA 1	Groups			p-level
	N	SG n=50	CG n=50	
Mild anxiety	39	24 (48%)	15 (30%)	X2=5.2 p=0.16
Mild to moderate anxiety	40	18 (36%)	22 (44%)	
Moderate to severe anxiety	15	7 (14%)	8 (16%)	
Severe anxiety	6	1 (2%)	5 (10%)	

X^2 (Pearson Chi-square)

Comparison of HAMA scores for assessment of anxiety is given in Table 4. It helps in estimating the speed of onset by which the effects of antidepressant treatment can be seen, that is, it enables to see the difference in the onset of the treatment efficacy in SG patients *versus* CG patients. This correlation was made in order to determine eventual difference in the efficacy of neurofeedback method as complementation to the pharmacological treatment in the study group against the effect of the drugs administered in the control group as monotherapy. The scores are shown as numerical values and percentages.

During the first follow-up assessment, a significant decrease in the HAMA scores was registered in the SG compared to the CG. The average HAMA score shows a significant decrease, by 2.86 points in the SG (p<0.0001), and by 0.84 points in the CG (p=0.0017). Percentage decrease in the HAMA score was by 13.72% points in the SG, and by 3.78% points in the CG.

Table 4. Total score on HAMA scale baseline/first follow-up assessment

HAMA score	SG n=50		CG n=50	
	Baseline	First follow-up assessment	Baseline	First follow-up assessment
mean ±SD	20.84 ± 7.0	17.98 ± 6.8	22.20 ± 8.2	21.36 ± 8.3
difference	2.86		0.84	
p-level	t=11.96 p=0.00000		t=3.32 **p=0.0017	
% of change	13.72%		3.78%	

**sig p<0.01, ***sig p<0.0001

The result of the HAMA scale at the second follow-up assessment was significantly lower in the study group treated with antidepressants in combination with the neurofeedback method compared to the control group treated only with antidepressants (p=0.029, difference=3.32). In the study group (SG), the average score on this scale was 16.82 ± 6.7, while in the control group (CG) 20.14 ± 8.3 (Table 5)

Table 5. HAMA scale scores at second follow-up assessment

HAMA - 2	groups		p-level
	SG n=50	CG n=50	
mean ±SD	16.82 ± 6.7	20.14 ± 8.3	t=2.21 *p=0.029
min- max	4 – 36	5 – 45	

t(Student t-test)
*sig p<0.05

Comparative analysis by HAMD (Hamilton Depression Rating Scale)

The average HAMD score was 17.98 ± 5.7 in the SG and 18.42 ± 6.1 in the CG at baseline; there was no statistically significant difference between both groups (p=0.1) (Table 6).

Table 6. Total score on HAMD at baseline and first follow up assessment

HAMD 0 and HAMD 1	groups		p-level
	SG n=50	CG n=50	
HAMD 0 mean ±SD	17.98 ± 5.7	18.42 ± 6.1	t=0.37 p=0.71 t=2.32 *p=0.022
HAMD 0 min- max	7 – 34	7 – 32	
HAMD 1 mean ±SD	15.56 ± 5.4	18.30 ± 6.3	
HAMD 1 min- max	6 – 30	7 – 32	

t(Student t-test)
*sig p<0.05

Analyzing the HAMD scores tallied at baseline and during the first follow-up assessment (2 weeks after the initiation of treatment), the following results were obtained. At baseline, patients from the study group mostly had severe depression, followed by moderate depression (32% and 28%, respectively). Patients from the control group mostly had moderate depression followed by very severe depression (34% and 28%, respectively).

No significant difference was found in the distribution of patients without depression, with mild, moderate, severe and very severe depression between both groups (p=0.44). Patients treated with antidepressants in combination with neurofeedback (SG) had significantly higher scores than patients treated only with antidepressants.

Table 6 illustrates scores measured during the first follow-up assessment. The average HAMD score was 15.56 ± 5.4 in the SG and 18.30 ± 6.3 in the CG; the difference of an average 2.74 scores was statistically significant for p=0.022.

Results obtained during the first assessment, in numerical and percentage values, are presented in Table 7.

Table 7. Distribution of patients by HAMD categories at first follow-up assessment

HAMA 1	Groups			p-level
	N	SG n=50	CG n=50	
No depression	3	2 (4%)	1 (2%)	X^2=7.9 p=0.096
Mild depression	25	15 (30%)	10 (20%)	
Moderate depression	35	21 (42%)	14 (28%)	
Severe depression	15	6 (12%)	9 (18%)	
Very severe depression	22	6 (12%)	16 (32%)	

X^2 (Pearson Chi-square)

Table 8 presents the correlation of HAMD scores obtained at baseline and during the first follow-up assessment in order to determine probable difference in the onset of antidepressant effect. The initial results demonstrated that scores measured in the SG were lower than those in the CG, suggesting that SG patients achieved faster onset of antidepressant effect compared to that in CG patients. Scores on the HAMD scale showed a significant decrease in the SG compared to the CG at the first follow-up assessment. The average HAMD score was significantly reduced by 2.42 points in the SG (p<0.0001), and non-significantly by 0.12 points in the CG (p=0.63). Percentage decrease in the HAMD score was by 13.46% in the SG, and by 0.65% in the CG.

Table 8. Total score on HAMD scale at baseline/first follow-up assessment – SG and CG

HAMA score	SG n=50		CG n=50	
	First examination	Second examination	First examination	Second examination
mean ±SD	17.98 ± 5.7	15.56 ± 5.4	18.42 ± 6.1	18.30 ± 6.3
difference	2.42		0.12	
p-level	t=15.44 ***p=0.000000		t=0.48 p=0.63	
% of change	13.46%		0.65%	

**sig p<0.01, ***sig p<0.0001

The result of the HAMD scale for depression on the second assessment was significantly lower in the group treated with antidepressants and the neurofeedback method compared to the group treated with antidepressants alone (p=0.0064, difference=3.06). In the SG, the average score on this scale was 14.50 ± 5.5, while in the CG it was 17.56 ± 6.2 (Table 9).

Table 9. Total score of HAMD scale at second follow-up assessment

HAMA - 2	groups		p-level
	SG n=50	CG n=50	
mean ±SD	14.50 ± 5.5	17.56 ± 6.2	t=2.8 **p=0.0064
min- max	4 – 28	6 – 31	

t(Student t-test)
*sig p<0.05

Discussion

Several clinical trials have been conducted in our country and in the region aimed at evaluating the efficacy of antidepressant drug therapy in the treatment of affective disorders[19]. This study is the first one in our country that has assessed the comparative efficacy between monotherapy with antidepressant drugs and a combined treatment with neurofeedback contributing to the growing body of research on alternative and adjunctive treatments for depression, particularly for those who do not achieve sufficient remission from standard pharmacological interventions. Given the high global prevalence of depression, its profound social and economic impact, and the substantial portion of patients experiencing treatment-resistant depression (TRD), exploring effective supplementary treatments like neurofeedback is essential.

This prospective randomized controlled study evaluated the efficacy of combined neurofeedback and pharmacological treatment *versus* antidepressant monotherapy in patients with affective disorders, focusing on depressive and anxiety symptoms. Our sample was demographically balanced, with a slight female predominance in both the study group (SG) and control group (CG), 52% and 54% in the study and in the control group respectively, consistent with findings in affective disorder epidemiology indicating a higher prevalence in women due to biological and psychosocial factors.

At baseline, both groups displayed comparable levels of depressive and anxiety symptoms on the HAMD and HAMA scales, with average total scores ranging 17.98 ± 5.7 in the SG and 18.42 ± 6.1 in the CG for HAMD, and 20.84 ± 7.0 in the SG, and 22.20 ± 8.2 in the CG for HAMA, indicating homogeneity before intervention. At the first follow-up assessment – two weeks after treatment initiation, the SG showed a significant reduction in both depression and anxiety scores compared to the CG, demonstrated by a statistically significant reduction in the total HAMD score by 2.42 points in the SG (p<0.0001), and non-significant 0.12 points reduction in the CG (p=0.63). As for the HAMA scale, the average score was

significantly reduced by 2.86 points or 13,72% in the SG ($p<0.0001$), and by 0.84 points or 3,78% in the CG ($p=0.0017$). This early improvement in the SG may highlight the potential of neurofeedback to accelerate therapeutic responses when used alongside medication. By the first follow-up, the average HAMD score in the SG dropped significantly, with more patients shifting from severe to moderate or mild depression, aligning with findings reported by Lee *et al*. (2019). They registered a significant decrease in the HAMD and CGI scores in the neurofeedback augmentation group when compared to those in the medication-only group, indicating that objective depressive symptoms and depression severity were further improved using neurofeedback when compared to medication-only[20].

At the second follow-up assessment, one month after the initiation of treatment, the SG continued to show marked improvements, with statistically lower HAMD and HAMA scores than the CG. The result of the HAMD scale for depression on the second assessment was significantly lower in the group treated with medication and the neurofeedback method compared to the group treated with antidepressants alone ($p=0.0064$, difference=3.06), with total average scores average score of 14.50 ± 5.5 in the SG, and 17.56 ± 6.2 in the CG. The efficacy of the combined treatment in the reduction of anxiety symptoms was further confirmed by the results from the HAMA scale on the second follow-up assessment, with statistically significant lower scores in the SG *vs*. the CG, 16.82 ± 6.7 for SG, and 20.14 ± 8.3 in the CG. This sustained effect supports the hypothesis that neurofeedback may enhance long-term outcomes in the treatment of depression by reinforcing neural regulation, as evidenced in a substantial body of literature incorporated in the recent meta-analysis by Xia *et al.* (2024) and the systematic review by Patil *et al.* (2023) that report neurophysiological improvements alongside the reduction in affective symptomatology[12,13]. This is in line with previous studies that demonstrate neurofeedback value in lowering symptom intensity in depressive patients who are not fully responsive to medication alone[20].

The results of our study align with the findings presented by Liu *et al.* and Patil *et al*., which demonstrated that neurofeedback contributed to significant symptom improvement in patients with depression[13,21]. Due to its non-invasive nature, minimal side effects, and relatively low cost, neurofeedback has emerged as a valuable adjunct of pharmacological treatments for affective disorders. Similarly, our findings are consistent with the conclusions of Dobbins *et al.* , who conducted a systematic review and noted that neurofeedback has recently gained prominence as an effective intervention for recurrent depressive disorder[22]. Many studies in their review emphasized neurofeedback's role in reducing depressive symptoms, reinforcing its potential as a promising non-pharmacological option. Collectively, these conclusions support the efficacy of neurofeedback observed in our study, highlighting its therapeutic value as an adjunctive treatment for individuals with treatment-resistant or recurrent depression.

Conclusion

The neurofeedback method is a well-established approach in treating patients with anxiety disorders as well as those with ADHD (Attention Deficit Hyperactivity Disorder). In recent years, it has increasingly emerged as a preferred method in treating patients with affective disorders. Additional research is needed to measure the efficacy of the neurofeedback method in treating patients with affective disorders, although initial results from our study are encouraging and motivate the inclusion of new patients. From the data we have processed so far, we can conclude that patients in the study group who were treated with medication therapy supplemented by the neurofeedback method showed lower scores on all scales used to quantify depressive and anxiety symptoms during the second assessment, compared to scores of participants in the control group who were treated with antidepressant monotherapy.

References

1. World Health Organization. Depressive disorder (depression). WHO. Available from: https://www.who.int/news-room/fact-sheets/detail/depression. Accessed 2024 Nov 10.
2. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, *et al.* A novel augmentation strategy for treating resistant major depression. Am J Psychiatry. 2001 Jan;158(1):131-4. doi: 10.1176/appi.ajp.158.1.131.
3. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, *et al.* Time for united action on depression: A Lancet-World Psychiatric Association Commission. Lancet. 2022;399(10328):957-1022. doi: 10.1016/S0140-6736(21)02141-3.
4. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. JAMA Netw Open. 2020;3(9):e2019686. doi: 10.1001/jamanetworkopen.2020.19686.
5. Albert P. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015;40(4):219-21. doi: 10.1503/jpn.150205.
6. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, *et al.* Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004;420:21-7. doi: 10.1111/j.1600-0047.2004.00327.x.
7. Heo M, Murphy CF, Fontaine KR, Bruce ML, Alexopoulos GS. Population projection of US adults with lifetime experience of depressive disorder by age and sex from year 2005 to 2050. Int J Geriatr Psychiatry. 2008 Dec;23(12):1266-70. doi: 10.1002/gps.2061. PMID: 18500691; PMCID: PMC3207493.
8. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Major depressive disorder: Developing drugs for treatment. Silver Spring: U.S. Food and Drug Administration; 2018.
9. European Medicines Agency. Clinical investigation of medici-

nal products in the treatment of depression – Scientific guideline. Amsterdam: European Medicines Agency; 2018.

10. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, *et al.* Treatment-resistant depression: Definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023;22(3):394-412. doi: 10.1002/wps.21120.
11. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, *et al.* The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J Clin Psychiatry. 2021;82(2):20m13699. doi: 10.4088/JCP.20m13699.
12. Xia Z, Yang PY, Chen SL, Zhou HY, Yan C. Uncovering the power of neurofeedback: a meta-analysis of its effectiveness in treating major depressive disorders. Cereb Cortex. 2024;34(6):bhae252. doi: 10.1093/cercor/bhae252.
13. Patil AU, Lin C, Lee SH, Huang HW, Wu SC, Madathil D, Huang CM. Review of EEG-based neurofeedback as a therapeutic intervention to treat depression. Psychiatry Res Neuroimaging. 2023;329:111591. doi: 10.1016/j.pscychresns.2023.111591.
14. Boessen R, van den Brink W, de Boer D, Gijsman HJ. Comparing HAMD17 and HAMD subscales on their ability to differentiate active treatment from placebo in randomized controlled trials. J Affect Disord. 2013;145(3):363-9. doi: 10.1016/j.jad.2012.08.026.
15. Carrozzino D, Bech P, Patrascu E, Moeller SB, Hofmann B, Tomba E. The Hamilton rating scales for depression: A critical review of clinimetric properties of different versions. Psychother Psychosom. 2020;89(3):133-50. doi: 10.1159/000506879.
16. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959 Mar;32(1):50-5. doi: 10.1111/j.2044-8341.1959.tb00467.x.
17. Jeong H, Lee B. Psychometric properties and factor structure of the Hamilton anxiety rating scale among Korean university students during COVID-19. Open Psychol J. 2024;17(1). doi: 10.2174/0118743501268244231108104216.
18. Asghar J, Arain SM, Hussain J, Bashir H, Iqbal R. A randomized clinical trial comparing two treatment strategies, evaluating the meaningfulness of HAMD rating scale in patients with major depressive disorder. Front Psychiatry. 2022;13:873693. doi: 10.3389/fpsyt.2022.873693.
19. Latas M, Stefanovski B, Mihaljević-Peleš A, Memić Serdarević A, Pajević I, Radulović NZ, *et al.* Diagnostic psychiatric and somatic comorbidity in patients with depression in the Western Balkan countries. PLoS ONE. 2024;19(1):e0295754. doi: 10.1371/journal.pone.0295754.
20. Lee YJ, Kim S, Lee WK, Choi J. Neurofeedback treatment on depressive symptoms and functional recovery in treatment-resistant patients with major depressive disorder: An open-label

pilot study. J Korean Med Sci. 2019;34(42):e287. doi: 10.3346/jkms.2019.34.e287.

21. Liu H. Neurofeedback training intervention for persons with major depression disorder: Reducing depressive symptoms. NeuroQuantology. 2017 Sep 7;15(3). doi: 10.14704/nq.2017.15.3.1091.

22. Dobbins ICS, Bastos M, Ratis RC, Silva WCFND, Bonini JS. Effects of neurofeedback on major depressive disorder: a systematic review. Einstein (Sao Paulo). 2023 Jul 21;21:eRW0253. doi: 10.31744/einstein_journal/2023RW0253.

CLINICAL SCIENCE

INFLUENCE OF VANCOMYCIN AND MEROPENEM LOADING ON COMPRESSIVE STRENGTH OF POLYMETHYL METHACRYLATE BONE CEMENT

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Key words: antibiotic-loaded bone cement, meropenem, vancomycin, compressive strength

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Abstract

The rise of antibiotic resistance of certain bacteria to commonly used agents in antibiotic- loaded polymethyl methacrylate (PMMA) bone cement has led to the search for new antibiotic agents. A potential problem in introducing new antibiotics into the PMMA mixture is disruption of the mechanical properties of bone cement, which is intended for mechanical fixation of joint implants. The aim of this study was to test compressive strength of bone cement loaded with vancomycin, meropenem or their combination. Materials and methods: Five groups of samples (PMMA, PMMA+2.5%w/w vancomycin, PMMA+2.5%w/w meropenem, PMMA+1.25%w/w vancomycin and 1.25%w/w meropenem and PMMA+2.5%w/w vancomycin and 2.5%w/w meropenem) were prepared and tested for compressive strength according to specifications of the ISO5833:2002 international standard. Results: All tested groups had compressive strength significantly above the minimum value of 70 MPa set by the standard (87.9 – 98.6MPa, p<.0001). All groups of antibiotic-loaded bone cement had significantly lower compressive strength than PMMA. Conclusion: All tested groups met the basic compressive strength criteria for clinical use in arthroplasty procedures.

КЛИНИЧКИ ИСТРАЖУВАЊА

ВЛИЈАНИЕ НА ВАНКОМИЦИНОТ И МЕРОПЕНЕМОТ ВРЗ МЕХАНИЧКИТЕ КАРАКТЕРИСТИКИ НА ПОЛИМЕТИЛМЕТАКРИЛАТЕН КОСКЕН ЦЕМЕНТ

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Цитирање: Поповска Д, Аврамов Н, Самарџиски М, Шабани И, БАндоновски А, Богојевска Докевска М, Стојменски С. Влијание на ванкомицинот и меропенемот врз механичките карактеристики на полиметилметакрилатен коскен цемент Арх Ј Здравје 2025;17 (1) 63 - 72.

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Клучни зборови: коскен цемент, ванкомицин, меропенем, максимална јакост на притисок

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Печатарски права: ©2025. Даница Поповска, Никола Аврамов, Милан Самарџиски, Илир Шабани, Алан Андоновски, Милена Богојевска Доксевска, Славчо Стојменски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Порастот на антибиотската резистенција на бактериите на вообичаените агенси кои се користат во полиметилметакрилатен (ПММА) цемент како метод за локално доставување на високи дози на антибиотик во ендопротетиката предизвикува интерес за воведување на нови антибиотици. Проблем при користењето на антибиотици е нарушувањето на механичките карактеристики на цементот. Целта на ова истражување беше процена на максималната јакост на компресија на коскен цемент со додадени различни количини ванкомицин и меропенем. Материјали и методи: Пет групи на примероци (чист ПММА, ПММА со 2,5% ванкомицин, ПММА со 2,5% меропенем, ПММА со 1,25% ванкомицин и 1,25% меропенем и ПММА со 2,5% ванкомицин и 2,5% меропенем) беа подготвени и тестирани за максимална јакост на притисок според спецификацијата на меѓународниот стандард ISO5833:2002. Резултати: Сите групи на тестирани примероци имаа значително поголема максимална јакост на притисок во однос на минимално одредената граница од 70 MPa (87.9 – 98.6MPa, p<.0001). Групите со додадени антибиотици имаа сигнификантно пониска јакост во однос на групата без антибиотик. Заклучок: Во однос на максималната јакост на притисок, сите испитани формулации во оваа студија ги задоволуваат основните критериуми за клиничка употреба при процедурите на артропластика.

Introduction

Antibiotic loading of polymethyl methacrylate (PMMA) bone cement is an established practice in joint replacement surgery. Gentamycin-loaded PMMA is commercially available from numerous brands. Prophylactic use of antibiotic-loaded bone cement (ALBC) has become more frequent due to the results of studies based on the Norwegian arthroplasty register, which showed that combined use of systemic antibiotic and ALBC for implant fixation in total hip replacement leads to lower revision rates compared to using systemic antibiotic or ALBC alone.[1,2] Many studies indicate that the revision risk for total hip arthroplasty is similar for cemented and non-cemented implants, but the risk is higher for cemented implants where bone cement without antibiotics is used.[3–5]

The increasing prevalence of multiresistant bacterial strains causes decrease in the efficacy of established ALBC preparations containing gentamycin. Therefore, there is interest in developing ALBC with different antibiotic combinations.[6,7] One of the challenges of adding antibiotics to bone cement is alteration of mechanical properties of the cement, which are critical when used for implant fixation.[8] The International Organization for Standardization (ISO, Geneva, Switzerland) defines compressive strength as one of the key indicators of the mechanical properties of polymerized cements, setting a requirement that all commercially available bone cements must withstand a compression force of at least 70 MPa.[9]

The aim of this study was to test the compressive strength of bone cement loaded with vancomycin, meropenem or their combination, and to determine whether the tested combinations meet the compressive strength requirements for use in implant fixation.

Materials and methods

We conducted an experimental study, in which we tested the compressive strength of the commercially available bone cement Smart Set Endurance™ MV (DePuy Synthes) loaded with vancomycin and meropenem for intravenous use in powder form. All tested samples were manufactured from the same cement series with LOT number 3684077. We produced and tested five groups of samples with the following antibiotic combinations:

1. PMMA group – control group without antibiotic
2. V 2.5% - 40 g PMMA with 1 g vancomycin
3. M 2.5% - 40 g PMMA with 1 g meropenem
4. VM 2.5% - 40 g PMMA with 0.5 g vancomycin and 0.5 g meropenem
5. VM 5% - 40 g PMMA with 1 g vancomycin and 1 g meropenem

For all groups of samples, we tested the compressive strength as the maximum compressive force before plastic deformation of cylindric specimens occurs, following the instructions of the ISO5833:2002, Annex E - Determination of compressive strength of polymerized cement.[9]

We prepared a total of 50 samples, with 10 samples per each group. We prepared the bone cement ac-

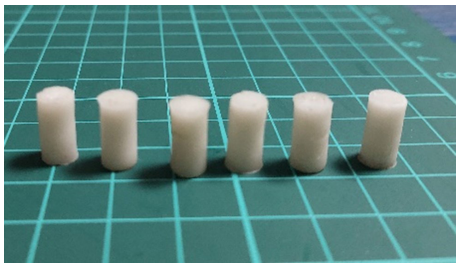
cording to packaging instructions. Cement mixing was performed in sterile conditions, at a temperature of 23±1°C. In all groups containing antibiotics, the powder component of the bone cement was mixed with the antibiotic powder and then the liquid component of the cement was added. The mixture was stirred with a spatula until a gloved finger with a sterile unpowdered latex glove separated cleanly from the cement. Then stainless-steel moulds (Figure 1 A.) were filled with the cement dough and clamped with end plates. After one hour of cement setting, the molds were unclamped, the excess cement was removed with an abrasive, and the specimens were removed with removal rods.

The samples for compressive strength testing were cylinders of length 12 (±0.1) mm and diameter 6 (±0.1) mm (Figure 1). They were stored in air for 24 hours, at a temperature of 23±1°C. Six samples were discarded due to visible defects in shape and filling. The average diameter of each test piece was measured, taking the measurements in two mutually perpendicular directions for two sections. This data was used to calculate the average diameter, sample surface, and volume. All samples were weighted, and density was calculated as the ratio of mass to volume.

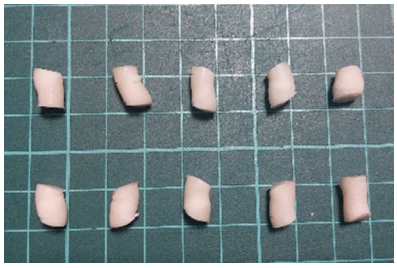
Figure 1. A. Molds for sample preparation. B. Cylindrical samples with 6 mm diameter and 12 mm height, group PMMA. C. VM 2.5% samples after testing



A.



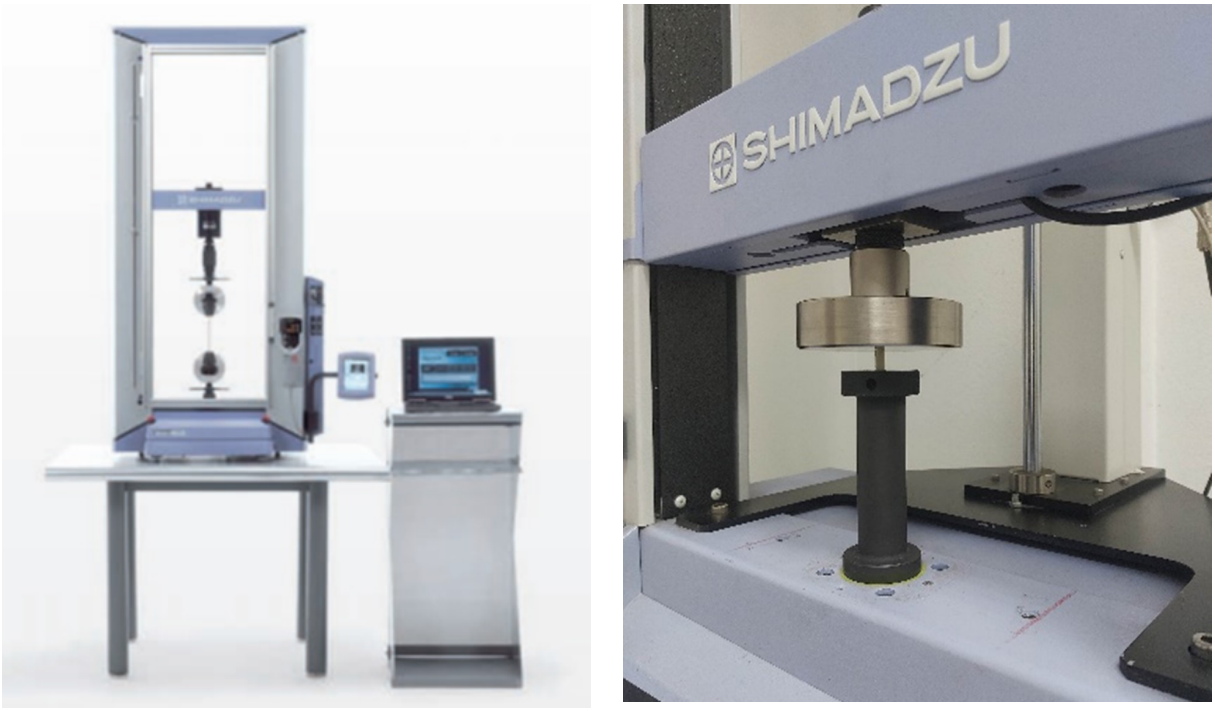
B.



C.

Compressive strength was tested for the remaining 44 samples at the Laboratory for material testing at Faculty of Mechanical Engineering, Ss. Cyril and Methodius University in Skopje using Shimadzu AGS-X 10kN materials testing machine with a speed range 0.001 to 1000 mm/min (Figure 2). The testing was performed at a cross-head rate of 23 mm/min. Data on force (N) and stroke (mm) were collected and compressive strength was calculated in MPa (N/mm^2). Figure 3 shows the output of the testing machine with the compressive strength graph. Two samples (from groups V 2.5% and M 2.5%) were ejected of the machine during compression, and results for these samples were excluded from the analysis.

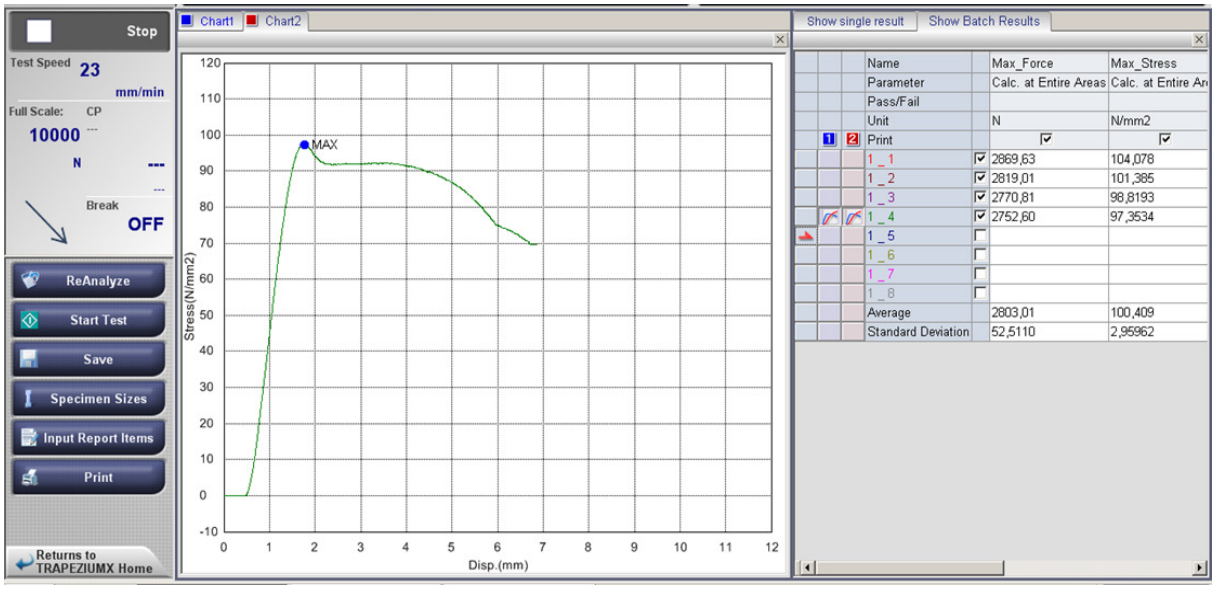
Figure 1. A. Shimadzu AGS – X materials testing machine. B. A sample set for testing in the materials testing machine



A. B.

The data were analyzed for a total of 42 samples with XLStat software for Excel (Lumivero (2024). XLSTAT statistical and data analysis solution. https://www.xlstat.com/en.) The results were examined with one-sample t-tests and analysis of variance (ANOVA) with post-hoc tests. We used alpha level of .05 for all statistical tests.

Figure 3. Output with graph for force/stoke relationship for sample 4 from PMMA group



Results

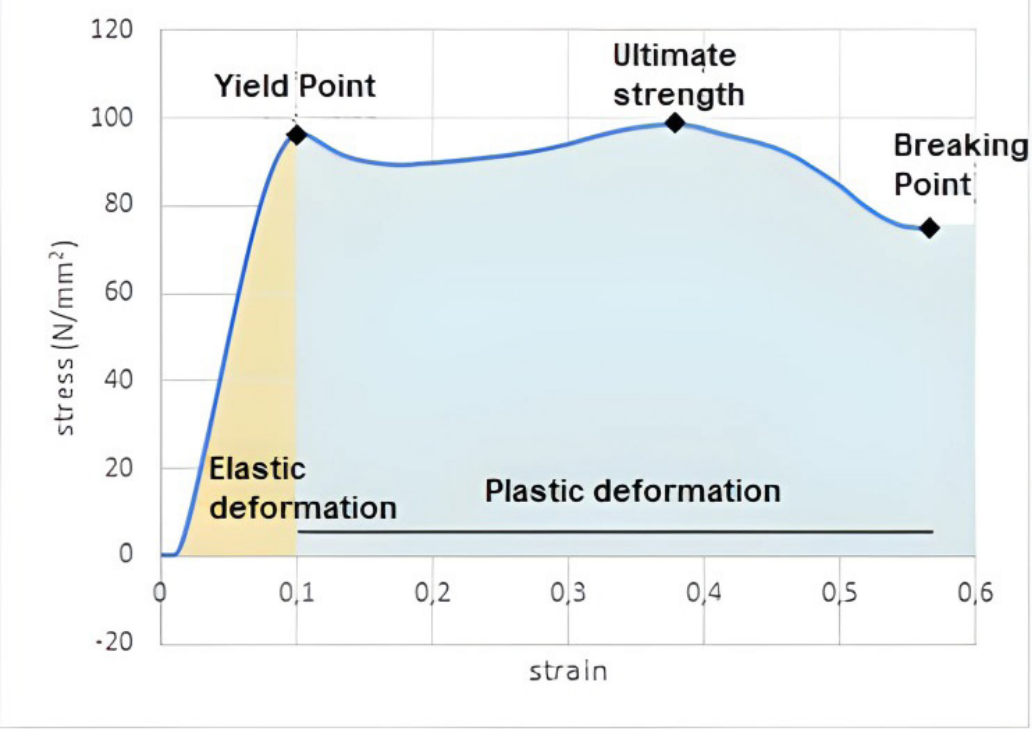
The average density of tested samples is shown in Table 1. All groups had normal distribution, as shown by the Shapiro-Wilk test. A one-way ANOVA revealed no statistically significant difference in density between at least two groups (F=1.831, p = .077), showing the homogeneity of specimen production.

Table 1. Sample density (mg/mm^3)

Group	N° of samples	Average density (mg/mm^3)	SD	Shapiro-Wilk P value
PMMA	8	1.216	0.042	0.993
V 2.5%	8	1.187	0.047	0.246
M 2,5%	8	1.173	0.052	0.551
VM 2.5%	10	1.202	0.017	0.116
VM 5%	8	1.188	0.030	0.517

The stress/strain relationship for sample 3 from PMMA group is presented in the graph in Figure 4 as a typical example of sample behavior. The first part of the graph curve is linear and represents the elastic sample deformation. When the strain of the yield point is reached, the stress begins to decrease and then a significant plastic deformation with a slight stress increase occurs until the sample breaks. The analysis of the compressive strength was performed with the yield point values, as they either coincide with or occur prior to the breaking point.

Figure 4. Stress/strain relationship for sample 3 from PMMA group

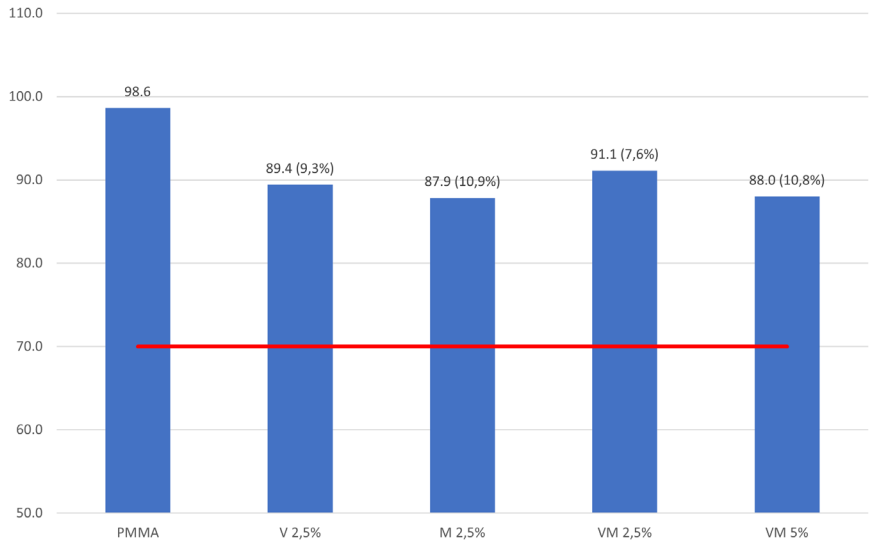


The average compressive strength was significantly above the threshold of 70 MPa in all examined groups (one sample t test, p<0.0001 for all groups). The percentage values above each column in Figure 5 represent the relative decrease in the compressive strength of ALBC groups compared to PMMA.

The Shapiro-Wilk test showed a normal distribution of data across all groups (p>.05 for all groups), and there was homogeneity of variances (Levene's test F=1.575, p=.201).

There were statistically significant differences between group means as determined by one-way ANOVA (F (4.37) = 19.377, p <.0001). Coefficient of determination R^2 was 0.68, suggesting that 68% of the compressive strength variance can be attributed to antibiotic addition.

Figure 5. Average compressive strength of all examined groups. Red line: Minimum acceptable value according to ISO5833



Post hoc comparisons using the Tukey HSD test indicated that the mean score for PMMA was significantly different than that in the groups with added antibiotics. However, no significant differences were observed among ALBC groups (Table 2). The minimum significant difference was 4.7 MPa.

Table 2. Tukey HSD comparisons

Contrast	Difference	Standardized difference	Critical value	p	Significant	Lower bound (95%)	Upper bound (95%)	Lower bound (95%)	Upper bound (95%)
PMMA vs M 2.5%	10.779	7.277	2.867	<0.0001	Yes	6.754	14.804		
PMMA vs VM 5%	10.618	8.520	2.867	<0.0001	Yes	6.593	14.643		
PMMA vs V 2.5%	9.206	5.617	2.867	<0.0001	Yes	5.181	13.230		
PMMA vs VM 2.5%	7.505	5.194	2.867	<0.0001	Yes	3.480	11.530		

VM 2.5% vs M 2.5%	3.274	2.613	2.867	0.158	No	-0.751	7.299		
VM 2.5% vs VM 5%	3.113	3.231	2.867	0.196	No	-0.911	7.138		
VM 2.5% vs V 2.5%	1.701	1.185	2.867	0.745	No	-2.324	5.725		
V 2.5% vs M 2.5%	1.573	1.069	2.867	0.795	No	-2.452	5.598		
V 2.5% vs VM 5%	1.413	1.143	2.867	0.851	No	-2.612	5.437		
VM 5% vs M 2.5%	0.161	0.158	2.867	1.000	No	-3.864	4.185		

q studentized range statistic: 4.054

Minimum significant difference: 4.721

Discussion

PMMA polymerization creates chemical bonds that determine its mechanical properties. Antibiotic molecules do not participate in the polymerization chain reaction; therefore, their presence in the polymer matrix decreases its mechanical performance. *In vitro* studies have shown a significant decrease in the compressive strength of bone cement loaded with cefazoline, cefuroxime, ceftazidime, meropenem, vancomycin, clindamycin and gentamycin, with clindamycin and gentamycin causing decrease below the minimal values necessary for weight bearing.[10]

Double antibiotic loading of bone cement is considered to have multiple benefits. Studies examining bone cement loaded with vancomycin and a second antibiotic showed that the addition of the second antibiotic improved vancomycin release. This is explained by the phenomenon of "passive opportunism", meaning that the release of the first antibiotic creates voids in the cement, which in turn facilitate the release of the second antibiotic.[7,11] Combining two antibiotics broadens the antibacterial spectrum of the ALBC. Numerous studies have investigated ALBC with different antibiotic combinations and found greater efficiency of antibiotic combinations in bacterial growth inhibition and reduction of infection incidence.[12] A study of 848 patients with hip fracture treated with hemiarthroplasty showed significantly lower incidence of deep infections in patients who received bone cement loaded with gentamycin and clindamycin compared to those who received ALBC with gentamycin only.[13] In another study that tested *in vitro* bacterial growth inhibition, ALBC samples containing vancomycin inhibited all Gram-positive bacteria, and when meropenem was added, inhibition of *E. coli* and *P. aeruginosa* was also observed.[14]

In this study, we examined the compressive strength of different antibiotic combinations that could potentially be used for primary and secondary infection prevention in arthroplasty. The compression test evaluates the maximum compressive force before the plastic deformation of cylindric specimens occurs. Compressive strengths of commercially available bone cements differ depending on their brand and composition, and range commonly between 80 and 100 MPa.[15] However,

all commercially available ALBCs must meet the ISO requirement to withstand a compression force of at least 70 MPa.

In our study, all ALBC groups had significantly lower compressive strength compared to antibiotic-free PMMA. All tested groups had an average compressive strength significantly above the threshold of 70 MPa set by the ISO5833. Persson *et al.* also tested ALBC with different doses of vancomycin and meropenem and found no significant decrease in the compressive strength compared to antibiotic-free control, although there was some reduction in the compressive strength in all ALBC groups.[16] The discrepancy with our findings may be attributed to differences in cement and antibiotic brands that may influence some of the variability of the bone cement compressive strength, since we found that only 68% of the compressive strength variability could be attributed to antibiotic addition.

Lilikakis and Sutcliffe tested various cement brands loaded with vancomycin of 2.5% w/w, 5%w/w and 10% w/w. They found that all tested doses caused a significant drop in the compressive strength of all examined brands, with most values being significantly above 70 MPa. Only the 10% w/w dose had a compressive strength of 74.55 MPa, and did not significantly differ from the threshold of 70 MPa.[17] Wang *et al.* found that meropenem can be added to bone cement in doses up to 15% of weight without significantly altering its mechanical properties, while establishing antibiotic release for 24 days at 37°C.[18] According to them, high doses of vancomycin (5%, 10%) lower the compressive strength of bone cement below 70 MPa.

In this study, we did not have the resources to test different cement brands. Although we expect that trends in mechanical properties changes would remain the same across different brands, the magnitude of changes may differ, as shown in the study of Lilikakis and Sutcliffe.[17] Using these antibiotic doses with different cement brands, especially at the highest dose, should be undertaken with caution. Investigation of different brands with the same antibiotic doses may show the magnitude of differences between them and their clinical significance.

In conclusion, meropenem and vancomycin loading decreases the compressive strength of bone cement. However, all tested doses meet the compressive strength requirements set by the international standard. Therefore, they may be considered for use in arthroplasty procedures in high-risk patients, particularly for secondary prevention in patients where infection was caused by susceptible organisms.

References

1. Espehaug B, Engesaeter LB, Vollset SE, Havelin LI, Langeland N. Antibiotic prophylaxis in total hip arthroplasty. Review of 10,905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987 to 1995. J Bone Joint Surg Br. 1997;79(4):590-595. doi:10.1302/0301-620X.79B4.7420

2. Engesæter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI. Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic

prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register. Acta Orthop Scand. 2003;74(6):644-651. doi:10.1080/00016470310018135

3. Engesæter L, Espehaug B, Lie S, Furnes O, Havelin L. Does cement increase the risk of infection in primary total hip arthroplasty? Revision rates in 56,275 cemented and uncemented primary THAs followed for 0-16 years in the Norwegian Arthroplasty Register. Acta Orthop. 2006;77(3):351-358. doi:10.1080/17453670610046253

4. Kunutsor SK, Beswick AD, Whitehouse MR, Blom AW, Lenguerrand E. Implant Fixation and Risk of Prosthetic Joint Infection Following Primary Total Hip Replacement: Meta-Analysis of Observational Cohort and Randomised Intervention Studies. J Clin Med. 2019;8(5). doi:10.3390/JCM8050722

5. Sebastian S, Liu Y, Christensen R, Raina DB, Tägil M, Lidgren L. Antibiotic containing bone cement in prevention of hip and knee prosthetic joint infections: A systematic review and meta-analysis. J Orthop Transl. 2020;23:53-60. doi:10.1016/J.JOT.2020.04.005

6. Neu HC. The crisis in antibiotic resistance. Science. 1992;257(5073):1064-1073. doi:10.1126/SCIENCE.257.5073.1064

7. Cerretani D, Giorgi G, Fornara P, et al. The in vitro elution characteristics of vancomycin combined with imipenem-cilastatin in acrylic bone-cements: a pharmacokinetic study. J Arthroplasty. 2002;17(5):619-626. doi:10.1054/ARTH.2002.32184

8. Hanssen AD. Prophylactic use of antibiotic bone cement: an emerging standard--in opposition. J Arthroplasty. 2004;19(4 Suppl 1):73-77. doi:10.1016/J.ARTH.2004.04.006

9. International Organization for Standardization ISO 5833:2002(en) Implants for surgery — Acrylic resin cements. 2002. https://www.iso.org/standard/30980.html. Accessed September 27, 2021.

10. Fleaca R, Mitariu SIC, Oleksik V, Oleksik M, Roman M. Mechanical behaviour of orthopaedic cement loaded with antibiotics in the operation room. Mater Plast. 2017;54(2):402-407. doi:10.37358/MP.17.2.4860

11. Penner MJ, Masri BA, Duncan CP. Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. J Arthroplasty. 1996;11(8):939-944. doi:10.1016/S0883-5403(96)80135-5

12. Blersch BP, Barthels M, Schuster P, Fink B. A Low Rate of Periprosthetic Infections after Aseptic Knee Prosthesis Revision Using Dual-Antibiotic-Impregnated Bone Cement. Antibiot 2023;12(9):1368. doi:10.3390/ANTIBIOTICS12091368

13. Sprowson AP, Jensen C, Chambers S, et al. The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip the fractured hip infection trial. Bone Jt J. 2016;98-B(11):1534-1541. doi:10.1302/0301-620X.98B11.34693

14. Baleani M, Persson C, Zolezzi C, Andollina A, Borrelli AM, Tigani D.

Biological and biomechanical effects of vancomycin and meropenem in acrylic bone cement. J Arthroplasty. 2008;23(8):1232-1238. doi:10.1016/j.arth.2007.10.010

15. von Hertzberg-Boelch SP, Luedemann M, Rudert M, Steinert AF. PMMA bone cement: Antibiotic elution and mechanical properties in the context of clinical use. Biomedicines. 2022;10(8). doi:10.3390/BIOMEDICINES10081830

16. Persson C, Baleani M, Guandalini L, Tigani D, Viceconti M. Mechanical effects of the use of vancomycin and meropenem in acrylic bone cement. Acta Orthop. 2006;77(4):617-621. doi:10.1080/17453670610012692

17. Lilikakis A, Sutcliffe MPF. The effect of vancomycin addition to the compression strength of antibiotic-loaded bone cements. Int Orthop. 2009;33(3):815. doi:10.1007/S00264-008-0521-3

18. Wang LH, Feng YD, Zhang XW, Jin L, Zhou FL, Xu GH. Elution and biomechanical properties of meropenem-loaded bone cement. Orthop Surg 2021;13(8):2417-2422. doi: 10.1111/os.13139.

CLINICAL SCIENCE

THE EFFECT OF WIDE SWADDLING ON ALPHA HIP ANGLE IN NEWBORNS AND INFANTS

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Abstract

Developmental dysplasia of the hip (DDH) is one of the most common diseases of the musculoskeletal system. Hip dysplasia occurs in 1:100, which means that it is 10 times more common than hip dislocation. The position of flexion and abduction in newborns and infants is the most common recommendation to improve hip development. The aim of this research is to evaluate the effects of wide swaddling, i.e., to determine whether wide swaddling influences hip maturation in the first months after birth and whether it has an effect on increasing the alpha angle of the hip during ultrasound examination. Materials and methods:

A prospective, clinical, stratified study was conducted on male and female newborns and infants with type Ia, Ib and IIa hip according to the Graf method. The subjects were divided into two groups. The first group included 20 newborns and infants using wide swaddling (40 hips monitored). The second group consisted of 23 newborns and infants who were not swaddled (46 hips monitored). The wide swaddling method involved using an additional cloth diaper and one wide swaddle diaper. Subjects underwent hip ultrasound according to the Graf method during the first hip examination at 4-8 weeks of age, and again two months after the initial assessment. Results: a simple procedure such as wide swaddling influences an increase in the alpha angle of the hip. There is an effect on hip development with faster transition from type IIa to type I according to the Graf method. After two months, the progression of hip maturation in the swaddling group was evident, while hips in the non-swaddling group remained type I and II, indicating that there is also a normal maturation in the other group. Further research is necessary to evaluate the long-term effects of wide swaddling on hip development.

КЛИНИЧКИ ИСТРАЖУВАЊА

ЕФЕКТОТ НА ШИРОКИОТ ПОВОЈ ВРЗ АЛФА АГОЛОТ КАЈ НОВОРОДЕНЧИЊА И ДОЕНЧИЊА

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Клучни зборови: развојна дисплазија на колк, ехосонографија, Граф, превенција, широк повој

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Печатарски права: ©2025. Марина Комненовиќ, Зоран Божиновски , Даниела Георгиева, Илир Шабани, Милена Богојевска-Доксевска, Дејан Дамјановиќ, Игор Атанасовски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Развојната дисплазија на колкот (РДК) е едно од најчестите заболувања на мускуло-скелетниот систем. Дисплазијата на колкот се јавува на 1:100 што значи дека е 10 пати почеста од дислокацијата на колкот. Физиолошкиот развој на колкот за време на растот е детерминиран од централната поставеност на феморалната глава во ацетабулумот. Задржувањето на колковите кај новороденчињата во положба на флексија и абдукција е најчестата препорака за подобрување на развојот на колкот. Цел на ова истражување е да се утврдат ефектите од користењето на широкиот повој, односно да се одреди дали широкиот повој има ефект врз зголемување на алфа аголот на колкот кај новороденчињата и доенчињата во првите месеци од раѓањето и да се утврди дали влијае врз поврз развој на колкот. Материјали и методи: Спроведена е проспективна клиничка стратифицирана студија во која испитаници се машки и женски новороденчиња и доенчиња со тип Ia, Iб и IIa колк според методот Граф. Испитаниците беа поделени во две групи. Првата група од 20 новороденчиња и доенчиња користеше широко повивање (следени 40 колкови). Втората група од 23 новороденчиња и доенчиња не користеа широко повивање (следени 46 колкови). Широкиот повој се состоеше од дополнителна тетра и шведска пелена за широко повивање. Испитаниците се следеа ехосонографски по методата на Граф на првиот преглед кој се направи на возраст од 4-8 недели и вториот преглед по два месеци. Промените во алфа аголот на двете групи се следеа и се направи споредба. Резултатите покажуваат дека едноставен третман како користење широк повој има ефект врз зголемување на алфа аголот на колкот. Широкиот повој има ефект врз развојот на колкот да премине од тип IIa кон тип I по методот на Граф. По два месеци може да се види прогресија во созревањето на колковите во групата која користи широк повој, но и колковите од групата која не користи широк повој сè уште се тип I и II според методот на Граф што значи дека има нормално созревање на колкот и во таа група. Потребно е дополнително проучување и следење на долгорочните ефекти од користењето на широкиот повој.

Introduction

Developmental dysplasia of the hip (DDH) is one of the most common diseases of the musculoskeletal system. Hip dysplasia occurs at 1:100, which means that it is 10 times more common than hip dislocation. The femoral head and the acetabulum interact with each other in growth and evolution from the prenatal period onward. Physiological development of the hip during growth is determined by the central placement of the femoral head in the acetabulum.

Keeping the hips in flexion and abduction in newborns and infants is the most common recommendation to improve hip development.[1]

Swaddling in adduction and extension leads to tightness of the iliopsoas muscle, hamstrings, and abductor muscles, which leads to an increased hip dislocation. With 100 degrees of hip flexion, pressure in the acetabulum is reduced, and the dislocation force of the hamstrings is reduced.[2]

In African countries, where newborns and infants are held in a position of flexion and abduction, they do not develop hip dysplasia. This in contrast to some Asian countries, where, due to cultural differences, newborns are saddled with their legs in a position of extension and adduction, and this increases the risk of various degrees of hip dysplasia.[3-7]

In 1959, Judet and Gielis, for DDH prevention, placed all newborns in the position of flexion and abduction up to 4 months of age using an abduction orthosis. In the study by Klisic et al., the benefit of wide swaddling was especially confirmed by reducing the prevalence over the four years of the study period.[8,9]

In newborns, there is a certain degree of hip laxity after birth, and therefore swaddling in the abduction and extension position should not be used.4

It has been confirmed in a study of traditional Mongolian swaddling by Munkhtulga Ulziibat et al. that prolonged swaddling of infants with the legs in a position of extension and adduction leads to improper maturation and formation of the hip joint, and is a major contributing factor to developmental disorders of the hip.[5]

According to a study by Harcke et al. conducted on 30 newborns with suspected and documented DDH, it was shown that the subjects who used swaddling in the position of adduction and extension led to instability or hip dislocation, while in the subjects who used a safe swaddling position, i.e., a wide swaddle, there was no change in hip stability.[10]

The effectiveness of wide swaddling has never been verified.[1]

When dysplasia of the hip is diagnosed on an ultrasound examination, subsequent treatment is abduction and flexion of the hips with orthosis so that the femoral head is centered and acts as a stimulating factor for the acetabulum for its development. With hip flexion of 100 degrees, the pressure on the acetabulum is reduced and the dislocation force of the hamstrings is reduced.[11]

Attention must be paid to the so-called Ramsey's safe zone, which means that the abduction of the hip should not be greater than 70 degrees in order to avoid decreasing blood supply to the femoral head, which may increase the risk of avascular necrosis (AVN) of the hip.

Wide swaddling allows free movement of the lower limbs, while still improving the position of flexion and abduction, which is necessary for better development and maturation of the hip.

It is very important that it does not exceed abduction beyond 90 degrees, as this could impair femoral head circulation and increase the risk of AVN.[12]

In North Macedonia, general screening of hip development exists, and orthopedic examination and hip ultrasound are mandatory in the first 6–8 weeks. We are an endemic region for DDH, and recommendations for wide swaddling have been given, but its effectiveness is not proven.

Besides general screening, many newborns and infants were late for examination and hip ultrasound, and that's why they receive recommendations for wide swaddling in the newborn wards.

In the past, wide swaddling was more commonly practiced, but nowadays, many mothers are reluctant to use it.

One of the reasons is the lack of evidence for its effect on hip maturation, and doctor's recommendations differ from person to person.

The aim of this research is to verify the effects of wide swaddling, i.e., to determine whether wide swaddling influences hip maturation in the first months after birth, and whether the use of wide swaddling has an effect on increasing the alpha angle of the hip in ultrasound examination.

Materials and methods

A prospective clinical stratified study was conducted, in which subjects were newborns and infants with Type Ia, Ib, and IIa hips according to the Graf method. The subjects were divided into two groups. In the group that used wide swaddling, 20 subjects (5 male and 15 female) were monitored. In the group that did not use wide swaddling, 23 subjects (10 male and 13 female) were monitored. The progression of the alpha angle from the first to the second examination in both groups was assessed.

Types Ia and Ib hips were included to evaluate whether there would be greater progression of the alpha angle (exceeding 60 degrees) over time in the wide swaddling group compared to the non-swaddling group.

Type IIa represents a physiologically immature hip in infants younger than three months, characterized by an alpha angle below 59 degrees. Type IIa hips were included to assess whether wide swaddling would lead to faster hip maturation.

The two groups were compared to determine whether there was a statistically significant difference in alpha angle progression between the wide swaddling group and the non-swaddling group.

The wide swaddling consists of one extra cloth diaper and wide diaper for which parents have been instructed on how to use it properly. The Clinical history of all subjects was analyzed, including fetal position during regnancy, postural anomalies, birth weight, and vitamin D3 prophylaxis.

The swaddling group that met the inclusion criteria used wide swaddling for 24 hours. The wide swaddling was removed only to change the sanitary diaper and bathe the newborn and the infant.

The non-swaddling group used only a standard hygienic diaper.

Any subject older than 3 months of age that turns into IIb hip according to Graf's method is excluded from the research and treated according to the protocols.

Inclusion criteria were:

Newborns and infants with hip Type Ia, Ib and IIa according to Graf.

Singleton pregnancy, cephalic placement of the fetus, term newborns. New borns and infants younger than 3 months. Normal birth weight (2500- 4000 g) Negative family history of developmental hip dysplasia.

Negative clinical findings for hip instability, no adductor contractures, negative Ortolani and Palmén tests. Vitamin D3 prophylaxis on regular base.

Exclusion criteria were:

Newborns and infants that on hip sonographic examination are type IIb; IIc, IId, type III and IV hip according to Graf.

Twin pregnancy or pelvic positioning of the fetus, prematurely born. Newborns and infants older than 3 months. Low birth weight (under 2500 g). Positive family history of developmental hip dysplasia.

Positive clinical findings for hip instability, adductor contractures, positive tests for instability Ortolani and Palmén. Newborns and infants that don't have vit D3 prophylaxis on regular basis.

Clinical examinations were performed: assessment of hip position, presence of adductor contractures, and tests for hip instability including Ortolani and Palmén maneuvers.

Measurement of hip range of motion was performed using a goniometer. Ultrasound hip measurement, following Graf's method, was performed using a Sonoscape A6 ultrasound device equipped with a linear probe of 7.0–8.0 MHz. Hip sonographic examination following Graf's method was performed within the first 4–8 weeks after birth.

Newborns and infants were then monitored again after 2 months to assess whether the hips transitioned to Type Ia or Ib according to Graf's classification, or remained physiologically immature in both groups.

This follow-up also aimed to evaluate the progression of alpha angles in both hip types, particularly in Type I.

Three measurements form both hips were taken for each subject, and the mean value of the measured angles was taken, as well as measurement of the hip maturation time interval (from IIa to type I hip according to Graf's method).

According to Graf's method, the hip ultrasound examination is based on three points, and the classification is based on a combination of morphological and morphometric criteria as well as the age of the child. To acquire a correct measurement of the angles, we need to obtain three important morphological points: the bone part of the acetabulum, the iliac bone and the labrum.

Three basic lines are drawn: the basic bone line, the line of the bony part of the acetabulum and the line of inclination (the cartilaginous part of the roof of the acetabulum).

The alpha and beta angles are formed between these three lines, that togeth-

er with the age of the child are morphometric criteria for classification. Hips that have an alpha angle greater than 60 degrees are considered type I hip according to the Graf method, i.e. a mature hip. An infant with an alpha angle between 50 - 59 degrees and age under 3 months is considered type IIa hip according to the Graf method. Type IIa hips are considered physiologically immature hips and require follow-up and regular sonographic examinations until they spontaneously transition to a mature hip.[5, 13]

Results

Measurements of the alpha angle were conducted in 20 newborns and infants (40 hips) who used wide swaddling for a period of 2 months. The alpha angles from the first examination were compared with the angle from the second examination of 40 hips. Measurements were made in 23 newborns and infants (46 hips) who did not use a wide swaddle and alpha angles from the first examination were compared with the angle from the second examination of 46 hips.

The first and second exams of both hips in the wide saddling group and non-swaddling group are presented in pairs on their first and second exams of both hips. The average value of all hips was taken and are presented in pairs for both hips in both groups. (Table 1)

Table 1: Comparison of the alpha angle in subjects using wide swaddling on the first and second examination and comparison of the alpha angle in subjects not using wide swaddling on first and second examination

		Mean	N	Std. Deviation
Pair 1	With Swaddling –right first exam	63,80	20	3,10
	With Swaddling –right second exam	65,90	20	3,49
Pair 2	With Swaddling -left first exam	63,70	20	3,02
	With Swaddling -left second exam	65,80	20	2,52
Pair 3	Non-Swaddling-right first exam	66,08	23	3,02
	Non -Swaddling–right second exam	66,08	23	2,59
Pair 4	Non-Swadling-left first exam	65,65	23	2,40
	Non-Swaddling-left second exam	65,34	23	5,02

The average value of alpha angle in the group with wide swaddling for both hips on the first exam and after two months was compared. A progression in alpha angles for both hips of 2.1 degrees was registered. (Table 2)

Table 2: The average value from the first exam was compared with the second exam after two months of using wide swaddling.

	Average value		Average value
Alpha angle first exam right	63,8	Alpha angle first exam left	63.7
Alpha angle second exam right	65,9	Alpha angle second exam left	65
Difference in degrees	2,1	Difference in degrees	2,1
P value	0,0002	P value	0,006

The average value of alpha angle in non-swaddling group for both hips on the first exam and after two months was also compared. There was no progression in alpha angles. (Table 3)

Table 3: Comparison of the alpha angle in subjects in non-swaddling group

	Average value		Average value
Alpha angle first exam right	66,08	Alpha angle first exam left	65,65
Alpha angle second exam right	66,08	Alpha angle second exam left	65,34
Difference in degrees	0	Difference in degrees	0,31
P value	1,000	P value	0,770

Using paired sample test on right and left hips of wide swaddling group showed that there is significant difference between first and second exam after 8 weeks. (for swaddling group right hip t = 3,566, p < 0,05; left hip t =3, 070, p < 0,05).

The results showed that there is no significant difference in non-swaddling group between the first and second exam after 8 weeks. (for non-swaddling group right hip t = 0, 000, p>0,05|; left hip 0, 295, p>0,05).

Discussion

According to the study of Lee C.W. et al., double diapering resulted in a greater increase in the alpha angle, and more babies recovered to having bilateral Graf type I hips within 1 month compared to the natural maturation of newborn hips.

In this study, newborns with Graf type IIa hips were selected as subjects, as they are commonly observed to undergo maturation of the acetabular roof.[1]

A Graf type II hip is a physiologically immature hip that should be followed sonographically until transitioning to a type I hip. [9]

Swaddling into extension and adduction of the lower extremities increases the rate of hip instability.[5–7, 14]

Measurement of hip abduction and flexion angles is important because a certain degree of hip flexion and abduction has a stimulating effect on hip development.[3]

By placing the wide swaddle, greater hip flexion and abduction are achieved, which places the femoral head in a better position in the acetabulum and has a stimulating effect on its development. In the study by Rosendahl K., it was proven that patients who were treated with an abduction orthosis at the time of diagnosis of dysplasia had better and faster maturation of the hips than the group that was only monitored.[15]

Klisic, in his study “Effects on Triple Prevention for CDH,” shows that before the introduction of baby packages (which contain materials for wide diapering and are given to every new mother) in the period between 1975-1977, 202-208 new cases of DDH were registered each year (mean 221). After the introduction of baby packages, in the period between 1981-1985, there were only 69-90 new cases per year (mean 77), a reduction of 65%

was recorded.[8]

The results the study by Bing Liu et al. showed that during the first 3 months of life in newborns and infants, the alpha angle exhibits a monthly increase.[13]

The incidence of type IIa hips ranges from 5% - 12% according to the time of the ultrasound examination.

It has been reported that most cases with IIa hips spontaneously resolve when they get older. However, it is difficult to ascertain that all infants with Graf type IIa hips should be observed and evaluated for the natural course of type IIa hips using Graf perspective of physiological immaturity.[16]

Evidence that post-natal positioning may be responsible for DDH comes in the form of a higher incidence of DDH seen in populations which practice restrictive immobilization of the lower limbs of their infants (swaddling in adduction and extension).

Czeizel et al. reported that out of 18,219 live births in Bekes County, Hungary, between 1970 and 1972, 523 infants came for treatment of DDH. Apart from genetic factors, the authors attributed this unusually high incidence of 28.7 per 1000 live births to unhealthy restrictive swaddling practices then prevalent in the studied population.[14]

Ulziibat M et al. conducted a study with two groups, one that used traditional Mongolian swaddling (with legs in adduction and extension) and one no swaddling group.

The follow up lasted one month (it was not allowed to continue the swaddling more than 1 month for the study purpose because of the Ethical Review Committee's recommendations).

In both groups type I and II a+, II a- hips were included.

The study provides evidence that traditional swaddling is a significant contributing factor for delayed maturation of the physiologically immature Type 2a hips and development of DDH. [5]

In the previous studies, swaddling groups (in adduction and extension) were compared with non-swaddling groups.

There are few studies that compared safe- wide swaddling (with lower extremities in abduction and flexion) with no swaddling group.

In our study, newborns and infants with type I and type IIa hips according to Graf's method were selected. A comparison was made between 40 hips in the group that used wide swaddling and 46 hips in the group that did not, with a follow-up period of 2 months.

It was determined that in the group that used wide swaddling, there was a significant increase in the alpha angle of the hip during the first two months of use.

The increase in the alpha angle from the first to the second examination was about 2.1 degrees for both hips, while in the subjects who did not use wide swaddling, there was no significant increase in the alpha angle after two months from the first examination.

After the comparison of the group that used wide swaddling between the first and second examination, there is a statistically significant difference ($p < 0.05$) compared to the group that did not use wide swaddling where there was no statistically significant difference in the alpha angle between

the first and second examinations ($p > 0.05$).

After the comparison of the group that used wide swaddling compared to the group that does not use it, it was determined that there is a significant difference in the increase of the alpha angle of the hip in patients that used a wide swaddling.

Compared to the Study from Lee and al. we have similar progression of alpha angle in the swaddling group. From the first examination at birth, they have mean progression after 1 month of +7, 9 in double diapering group. In the non-swaddling group from birth after one month they have progression of + 5, 2 degrees.[1]

The study by Raba A.A. and colleagues discusses and has a special focus on type IIa hips, where it's not possible to determine which hips will deteriorate or have a spontaneous evolution and that this should be investigated further, but as an independent warning factor it emphasizes that if the alpha angle at the first examination is less than 55 degrees then that hip has a negative predictive factor. [16]

In the study by Riad P. J and colleagues, subjects aged 6 to 12 weeks were followed and the progressions of alpha and beta angles as well as FHC were monitored and measured.

It was concluded that FHC alpha and beta angles change significantly over time, but it is important to take the age of the child into account when interpreting hip ultrasound findings.[17]

We need more follow up of this, because we need to distinct if there is an effect from wide swaddling on hip maturation and progression of alpha angle.

Some studies conclude that the hip in the first months of life had exponential growth and maturation with plateau in the 4-6 months of life.[13]

In our country, among the pediatric orthopedic surgeons, there is an ongoing lively discussion whether double diapering should be used or not. Most of the older orthopedic surgeons adhere strictly to the double diapering principle that roots from the Klisic conclusions, and their use is justified. Most of the younger orthopedic surgeons that are involved in the neonatal hip ultrasound screening, do not recommend wide diapering in type 2a+ or 1a/1b hips according Graf method. The positive effect from double diapering is concluded in this and many previous studies. It is also recommended in most neonatal wards in our country.

There is no consensus among the ones recommending wide diapering, and the recommendations differ from two hygienic diapers placed one above the other, one or two cloth diapers above the hygienic diaper, secured by a wide swaddle diaper or commercially available "wide diapering underpants". Also, there is no consensus on the duration of the wide diapering, some of us discontinue the use of the double diapering at the first ultrasound screening examination, that should be done by three months of the infant, or the second ultrasound examination screening, that is done at 6 months of age. Also, there are some studies that conclude that the diapering delays infant's milestones as sitting, crawling and walking.[18]

Conclusion

The results show that a simple treatment, such as wide swaddling, contributes to an increase in the alpha angle of the hip. The results also show that there is an effect on the development of the hip to go from type IIa to type I according to Graf's method.

After two months we can see the progression of hip maturation within the swaddling group, but the hips within the non-swaddling group are still type I and II according to Graf method that means we also have a normal maturation in the other group.

Regarding this fact we need further studies and monitoring of the long-term effects of using wide swaddling to determine whether it has effect on hip maturation and progression of alpha angle or it is spontaneous maturation with rapid progress in some hips.

References

1. Lee WC, Kao HK, Chen MC, Yang WE, Chu SM, Chang CH. Double diapering facilitates hip maturation in newborns. Pediatr Neonatol. 2022; 63(2):159–64. doi: 10.1016/j.pedneo.2021.06.021.
2. Yamamuro T, Ishida K. Recent advances in the prevention, early diagnosis, and treatment of congenital dislocation of the hip in Japan. Clin Orthop Relat Res. 1984; (184):34–40. doi:10.1097/00003086-198404000-00005.
3. De Pellegrin M, Damia CM, Marcucci L, Moharamzadeh D. Double diapering ineffectiveness in avoiding adduction and extension in newborns hips. Children. 2021; 8(3). doi. 10.3390/children8030179.
4. Vaidya S, Aroojis A, Mehta R. Developmental Dysplasia of Hip and Postnatal Positioning: Role of Swaddling and Baby-Wearing. Vol. 55, Indian Journal of Orthopaedics. Springer; 2020. p. 1410–6. doi: 10.1007/s43465-021-00513-3.
5. Ulziibat M, Munkhuu B, Bataa AE, Schmid R, Baumann T, Essig S. Traditional Mongolian swaddling and developmental dysplasia of the hip: a randomized controlled trial. BMC Pediatr. 2021; 21(1). doi: 10.1186/s12887-021-02910-x.
6. Graham SM, Manara J, Chokotho L, Harrison WJ. Back-carrying infants to prevent developmental hip dysplasia and its sequelae: Is a new public health initiative needed? Vol. 35, Journal of Pediatric Orthopaedics. Lippincott Williams and Wilkins; 2015. p. 57–61. doi: 10.1097/BPO.0000000000000234.
7. Kotlarsky P, Haber R, Bialik V, Eidelman M. Developmental dysplasia of the hip: What has changed in the last 20 years? World J Orthop. 2015; 6(11):886–901. doi: 10.5312/wjo. v6. i11.886.
8. Klisić P, Zivanović V, Brdar R. Effects of triple prevention of CDH, stimulated by distribution of "baby packages". J Pediatr Orthop. 1988; 8(1):9–11. doi: 10.1097/01241398-198801000-00002.
9. Graf R. Classification of hip joint dysplasia by means of sonography. Arch Orthop Trauma Surg. 1984; 102(4):248–55. doi: 10.1007/BF00436138.
10. Harcke HT, Karatas AF, Cummings S, Bowen JR. Sonographic Assessment of Hip Swaddling Techniques in Infants with and Without DDH. J Pediatr Orthop. 2016; 36(3):232–8.

doi: 10.1097/BPO.0000000000000446.

11. Staheli LT. Management of congenital hip dysplasia. Pediatr Ann. 1989; 18(1):24, 26–7, 29–32. doi: 10.3928/0090-4481-19890101-06.

12. Liu YH, Xu HW, Li YQ, Hong K, Li JC, Pereira B, et al. Effect of abduction on avascular necrosis of the femoral epiphysis in patients with late-detected developmental dysplasia of the hip treated by closed reduction: A mri study of 59 hips. J Child Orthop. 2019; 13(5):438–44. doi: 10.1302/1863-2548.13.190045.

13. Liu B, Hu X, Li L, Gao S. Morphological development of the hip in normal infants under six months of age by the Graf ultrasound method. Front Pediatr. 2022; 10. doi: 10.3389/fped.2022.914545. 14. Czeizel A, Szentpetery J, Kellermann M. Incidence of congenital dislocation of the hip in Hungary. Brit J Prev Soc. Med. 1974; 8 doi: 10.1136/jech.28.4.265.

15. Rosendahl K, Markestad T, Lie RT. Ultrasound screening for developmental dysplasia of the hip in the neonate: the effect on treatment rate and prevalence of late cases. Pediatrics. 1994; 94(1):47–52.

16. Raba AA, Gasibat Q. Developmental Dysplasia of the Hip: Management of Graf IIa Dysplastic Hip. Open J Pediatr. 2020; 10(02):247–54. doi: 10.4236/ojped.2020.102025. 17. Riad JP, Cundy P, Gent RJ, Piotto L, Morris L, Hirte C. Longitudinal study of normal hip development by ultrasound. J Pediatr Orthop. 2005; 25(1):5–9. doi: 10.1097/00004694-200501000-00003.

18. Cole WG, Lingeman JM, Adolph KE. Go naked: diapers affect infant walking. Dev Sci. 2012; 15(6):783–90. doi: 10.1111/j.1467-7687.2012. 01169.x,

CLINICAL SCIENCE

COMPARISON OF THE EFFECTS OF HIGH-INTENSITY LASER WITH LOW-INTENSITY LASER IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Key words: high-intensity laser, low-intensity laser, knee osteoarthritis, WOMAC index

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Abstract

Knee osteoarthritis is a musculoskeletal disease characterized by degeneration and deterioration of articular cartilage. In addition to pharmacological therapy, physical modalities including low-intensity laser therapy (LILT) and high-intensity laser therapy (HILT), and kinesitherapy are used to treat knee osteoarthritis (KOA). To date, no research has been conducted in the Republic of North Macedonia that could be compared to existing research about the effects of HILT and LILT on functional ability in patients with KOA. The aim of this study was to compare the treatment effects of HILT and LILT in patients with KOA. Materials and methods: This was a randomized comparative single-blind study involving 72 patients divided into two groups. The first group was treated with 10 sessions of HILT, and the second group with 10 sessions of LILT. Patients of both groups performed exercises for 1 month. Functional outcome was evaluated after the end of the laser therapy and after 1 month using the Western Ontario and McMaster Universities Osteoarthritic Index (WOMAC). Statistical significance was defined as $p<0.05$. Results: At the end of the laser therapy and 1 month later, a statistically significant difference was found between the two groups, measured by the WOMAC index ($p<0.001$). Additionally, the WOMAC index was compared within the groups. Conclusion: Patients with KOA who were treated with HILT had significantly better functional recovery than patients treated with LILT.

КЛИНИЧКИ ИСТРАЖУВАЊА

СПОРЕДБА НА ЕФЕКТИТЕ ОД ЛАСЕР СО ВИСОК ИНТЕНЗИТЕТ И ЛАСЕР СО НИЗОК ИНТЕНЗИТЕТ КАЈ ПАЦИЕНТИ СО ОСТЕОАРТРИТИС НА КОЛЕНОТО

Валентина Коевска[1], Ериета Николиќ-Димитрова[1], Билјана Митревска[1], Цветанка Ѓеракароска-Савевска[1], Марија Гоцевска[1], Билјана Калчовска[1], Маја Манолева[1], Даниела Гечевска[1]

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Клучни зборови: високоинтензивен ласер, нискоинтензивен ласер, остеоартритис на колено, WOMAC индекс.

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Печатарски права: ©2025. Валентина Коевска, Ериета Николиќ-Димитрова, Билјана Митревска, Цветанка Ѓеракароска-Савевска, Марија Гоцевска, Билјана Калчовска, Маја Манолева, Даниела Гечевска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа ториганалниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Остеоартритисот на коленото е мускулно-скелетно заболување кое се карактеризира со дегенерација и влошување на зглобната ,рскавица. Покрај фармаколошката терапија, конвенционалните физикалните модалитети и кинезитерапија, во лекување на остеоартритис на коленото (ОАК) последниве неколку години се користи високоинтензивен ласер (ВИЛ) и нискоинтензивен ласер (НИЛ). Во нашата земја се уште немаше спроведено истражување каде е споредена ефектот на ВИЛ и НИЛ. Цел на трудот е да се спореди терапискиот ефект на ВИЛ со НИЛ во третманот на ОА на коленото. Материјал и методи: Рандомизирана компаративна едностранослепа студија која вклучува 72 пациенти поделени во две групи. Првата група се лекува со ВИЛ, втората група се лекува со НИЛ. Пациентите од двете групи изведуваа вежби во текот на 1 месец. Функционалниот исход беше оценет по завршувањето на ласерската терапија и по 1 месец со користење на остеоартритичниот индекс на универзитетите Западен Онтарио и Мекмастер (WOMAC). Статистичката значајност беше дефинирана како $p <0,05$. Резултати: На крајот од ласерската терапија и 1 месец подоцна, беше утврдена статистички значајна разлика помеѓу двете групи, мерена со WOMAC индексот ($p <0,001$). Дополнително, WOMAC индексот беше споредена во рамките на групите. Заклучок: Пациентите со КОА кои биле третирани со ВИЛ имале значително подобро функционално закрепнување од пациентите третирани со НИЛ.

Introduction

Osteoarthritis (OA) is a very common cause of chronic musculoskeletal pain and disability in the adult population. In fact, all people over 60 years have some degenerative changes in their joints; 70-85% of them have signs and symptoms such as pain and short-term morning stiffness. One of the most common forms of osteoarthritis found in clinical practice is knee osteoarthritis (KOA). Radiographic evidence of KOA is present in about 30% of men and women over the age of 65[1].

Knee osteoarthritis is characterized by degeneration and disintegration of the cartilage of the joint which over time leads to narrowing of the joint space. The ligaments and surrounding tendons may be affected. Pain, morning stiffness, and limited knee mobility are characteristic symptoms of OAK. Pain occurs due to changes in the synovial membrane, mechanical irritation from osteophytes, and extraarticular structures of the knee such as bursitis, tendinitis, tendinopathy, and etc. Pain and functional limitations lead to a reduction in quality of life and reduced participation in social activities[2].

Analgesics, nonsteroidal anti-rheumatic drugs, glucosamine sulfate, chondroitin sulfate, and regular exercising are recommended to reduce pain and improve functional ability[3]. So far, several physical modalities such as interference currents, diadynamic currents, laser treatment, therapeutic ultrasound, aquatic therapy, extracorporeal shockwave therapy, and pulsed electromagnetic field therapy have been shown to be effective in treating OAK pain[4, 5].

Several recent studies have shown that low-intensity laser therapy (LILT) reduces pain, stiffness and functional limitations in patients with OAK 6, 7. LILT has a biostimulatory effect, accelerates the regeneration of damaged and diseased tissues, reduces swelling and pain, and has an anti-inflammatory effect[7]. The advantage of these lasers is their minimal thermal effect. High-intensity laser (HILT) is a relatively new non-invasive physical modality in the treatment of OAK. The advantage of HILT is that by increasing power, the depth of penetration is increased, resulting in the augmented effects on deep structures. In tissues, HILT causes increased oxygenation in the mitochondria and formation of ATP, which leads to an increased absorption of edema by enhancing metabolism[8].

The HILT and LILT have been shown to have a biostimulative effect on cartilage, and surrounding muscle and ligament tissue in joints as well as a positive effect on pathoanatomical changes in OA. They also improve symptoms of the disease along with functioning. These effects were more pronounced when HILT was applied[9]. The results of several randomized trials investigating the effects of HILT treatment showed a significant reduction in pain and improvement in physical function in KOA[10,11,12,13].

So far, no comparative study of the impact of HILT and LILT on patients with knee OA has been conducted in North Macedonia. Therefore, we decided to initiate research in the local setting to evaluate the effects of this therapy, with the aim to implement a better and higher treatment quality in patients with KOA. The results of the research should help to

establish better treatment protocols for patients with KOA with physical therapy.

The aim of this study was to compare the treatment effects of HILT and LILT in patients with KOA.

Materials and methods

This single-blind randomized comparative study was conducted at the University Clinic for Physical Therapy and Rehabilitation in Skopje from January 2018 to March 2020. The study included 72 patients who had previously been diagnosed with KOA stage 1 and 2, based on X-ray.

Exclusion criteria were: application of corticosteroids and hyaluronic acid in the last 3 months, malignant diseases, fractures, tendon injury, meniscal injury, ligament injury, diseases of the hip and ankle, surgery of the knee, rheumatoid arthritis, diseases with contraindications for using laser therapy. Patients were randomly assigned in two groups.

Patients in group I were treated with high-intensity laser therapy, while patients in group 2 were treated with low-intensity laser therapy. For the high-intensity laser therapy, a VIKARE electro-medical device with 4W power was used. The treatment time per session was 10 minutes. The laser was applied by scanning transversally and longitudinally on the anterior, medial and lateral side of the knee joint with special emphasis on the femoral and tibial condyle. For the low-frequency laser treatment, an Eco Medico Laser device with 200mW power produced by Electronic Design was used. The total duration of one application was 8 minutes The patient lied in a supine position, with the knee flexed in 30º. Prior to application, the skin was cleansed with alcohol. The laser therapy was applied with a probe on the medial, anterior and lateral side of the knee, a total of 14 points. The patient and the doctor wore googles during the application of both LILT and HILT. Patients from both groups were treated daily, with a weekend break, receiving 10 sessions during a 2-week-period. In addition to laser therapy, patients of both groups performed strengthening and stretching exercises for knee and hip muscles every day for 30 minutes throughout the study period. Patients were evaluated before therapy, after 10 therapy sessions, and 1 month from the start of the therapy using the WOMAC index.

Assessment of physical function, stiffness, and knee pain was evaluated by the WOMAC index (Western Ontario and McMaster Universities Osteoarthritic Index). It consists of 24 items divided into three subscales: pain (5 items), stiffness (2 items), physical function (17 items). It can be used to monitor the course of the disease or to determine the effectiveness of various interventions (pharmacological, surgical, physiotherapy, etc.)[14].

The /study was approved by the Human Research Ethics Committee according to the Declaration of Helsinki, at the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, RN Macedonia and in compliance with the legal standards. Each patient was previously informed about the aims of the study, and signed an informed consent to participate. (No 03-2134/18)

The data obtained during the study was statistically processed using the SPSS Software Package, version 22.0 for Windows (SPSS, Chicago, IL, USA).

The analysis of the attributes (qualitative) series was done by determining the coefficient of relationships, proportions and rates, and they were shown as absolute and relative numbers. Numeric (quantitative) series were analyzed using central tendency measures (average, median, minimal values, maximum values, interactive rankings), as well as dispersion measures (standard deviation, standard error).

Pearson Chi Square Test, Fischer Exact Test and Fisher Feeman Halton Exact Test were used to determine the association between certain atrial dichotomic marks. Difference Test was used to compare the proportions.

Non-parametric tests for two independent specimens (Mann-Whitney U test) were used to test the significance of the difference between certain numerical parameters with improper frequency distribution. The analysis of two dependent numerical variables was made with Wilcoxon Signed Rank Test.

A level of P <0.05 was used to determine statistical significance.

Results

The mean age of patients in the HILT and LILT groups was 61.36 ± 8.14 vs. 60.36 ± 7.45 without a significant difference between the two groups (p = 0.71). Male patients were more prevalent in the group treated with HILT larger number of (p<0.05). No significant differences were found regarding mean age, number of patients in different age groups, and BMI (Table 1).

Table 1: General characteristics by groups

Parameters	groups		P
	HILT N=36	LILT N=36	
Gender N (%)			
Female	23 (63.89%)	31 (86.11%)	Pearson Chi-square test=4,74; df=1; p=0,0294*
Male	13 (36.11%)	5 (13.89%)	
Age(years)			
$\bar{X}$ ± **SD** **Min/Max** **Median (IQR)**	61.36±8.14 45/76 62 (55-68)	60.36±7.45 45/72 61 (55-66.5)	Mann-Whitney U Test: Z=0.37; p=0.71
Age groups - - N (%)			
40-49	2 (5.56%)	3 (8.33%)	Fisher-Freeman-Halton exact test: p=0.80
50-59	13 (36.11%)	14 (38.89%)	
60-69	13 (36.11%)	14 (38.89%)	
70-79	8 (22.22%)	5 (13.89%)	
BMI (kg/m²)			
$\bar{X}$ ± **SD** **Min/Max** **Median (IQR)**	30.68±4.49 22.25/40.40 30.24 (27.51-33.47)	30.29±4.49 22.55/40.40 29.38 (27.35-32.43)	Mann-Whitney U Test: Z=0.50; p=0.61

*Significant for p<0.05

The WOMAC subscales were analyzed at baseline, and after 10 therapy sessions. No significant baseline differences were found between the investigated groups (Table 2).

Table 2: Comparison of subscales from WOMAC between groups and within the group individually at two time points, 0 and 10 therapy sessions

WOMAC		N	X ± SD	Min/ Max	Median (IQR)	P
Pain						
0-time	HILT	36	14.39±3.31	9/20	15 (11-18)	[1]Z=0.99; p=0.32
	LILT	36	13.64±3.79	9/20	15 (10-16)	
10 therapies	HILT	36	4.44±2.28	1/10	4.5 (2.5-5.5)	[1]Z=-5.42; p=0.00001*
	LILT	36	8.28±2.46	4/15	8.5 (6-10)	
Wilcoxon signed rank test 0/10:				HILT - Z=5.21; p=0.00001* LILT - Z=5.06; p=0,00001*		
Stiffness						
0-time	HILT	36	6.36±1.42	3/8	7 (5.5-7.5)	[1]Z=0.03; p=0.96
	LILT	36	6.36±1.38	3/8	7 (6-7)	
10 therapies	HILT	36	1.50±0.94	0/4	1.5 (1-2)	[1]Z=-5.70; p=0.00001*
	LILT	36	3.55±1.31	0/6	4 (3-4.5)	
Wilcoxon signed rank test 0/10:				HILT - Z=5.23; p=0.00001* LILT - Z=5.15; p=0.00001*		
Function						
0-time	HILT	36	53.83±7.62	39/64	56 (47.5-60)	[1]Z=1.64; p=0.0001
	LILT	36	50.69±8.32	39/64	50 (43.5-58)	
10 therapies	HILT	36	24.50±9.78	9/38	24 (16-34)	[1]Z=-2.61; p=0.0088*
	LILT	36	30.94±6.61	16/44	32 (27-36)	
Wilcoxon signed rank test 0/10:				HILT - Z=5.23; p=0,00001* LILT - Z=5.23; p=0,00001*		
[1]Mann-Whitney U test				* significant for p<0.05		

Regarding pain, stiffness, and physical activity measured with the WOMAC subscales showed a significant reduction of all variables measured after 10 therapy sessions in both groups ($p<0.01$) (Figure 1). However, a significantly more pronounced effect regarding all analyzed variables was observed in the HILT group after 10 therapies (Table 2).

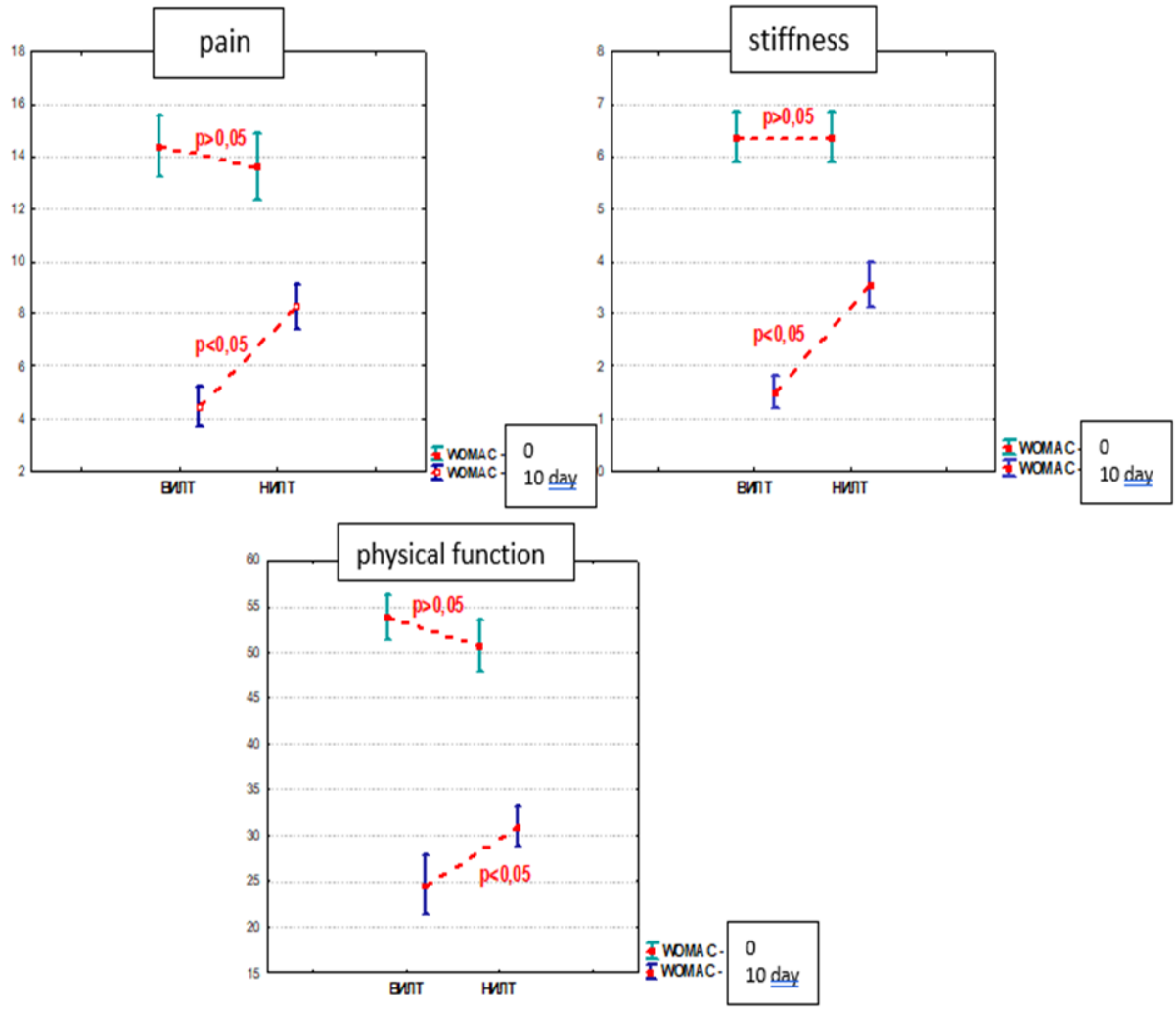


Figure 1: Comparison of WOMAC between groups and within the group individually at 0 and 10 day

The WOMAC index was assessed at baseline, after 10 therapies and after 1 month (Table 3). No significant difference was found between the two groups at baseline ($p<0.05$). A significant reduction of the WOMAC index was observed in both groups at both follow- ups compared to baseline. The maximum reduction of the WOMAC scale was noticed after 1 month (Figure 2). However, after 10 treatments a significant lower WOMAC index was observed in the HILT groups ($p<0.01$). This effect persisted and could also be observed at 1 month following therapy ($p<0.01$) (Table 3).

Table 3: Comparison of WOMAC between groups and within the group individually at three time points - 0, 10 days and 1 month

WOMAC		N	X ± SD	Min/ Max	Median (IQR)	P
0	HILT	36	74.58±10.54	55/88	78.5 (63.5-83.5)	[1]Z=1.4866; p=0.1371
	LILT	36	70.69±11.44	51/89	70 (62-79.5)	
10-Day	HILT	36	30.44±11.15	12/48	30.5 (21-40.5)	[1]Z=-4.3135; p=0.00002*
	LILT	36	42.78±8.11	25/59	44.5 (37.5-49)	
1-month	HILT	36	5.83±5.23	0/20	5.5 (1-9)	[1]Z=-7.2979; p=0.00001*
	LILT	36	40.75±9.37	22/58	40 (31-48)	
Friedman test 0/10/1 month, VILT- N=36; Chi-Square=72,011; df=2; p=0,00001* LILT -N=36; Chi-Square=53.535; df=2; p=0,00001*						
[1]**Mann-Whitney U test**			*significant p<0,05			

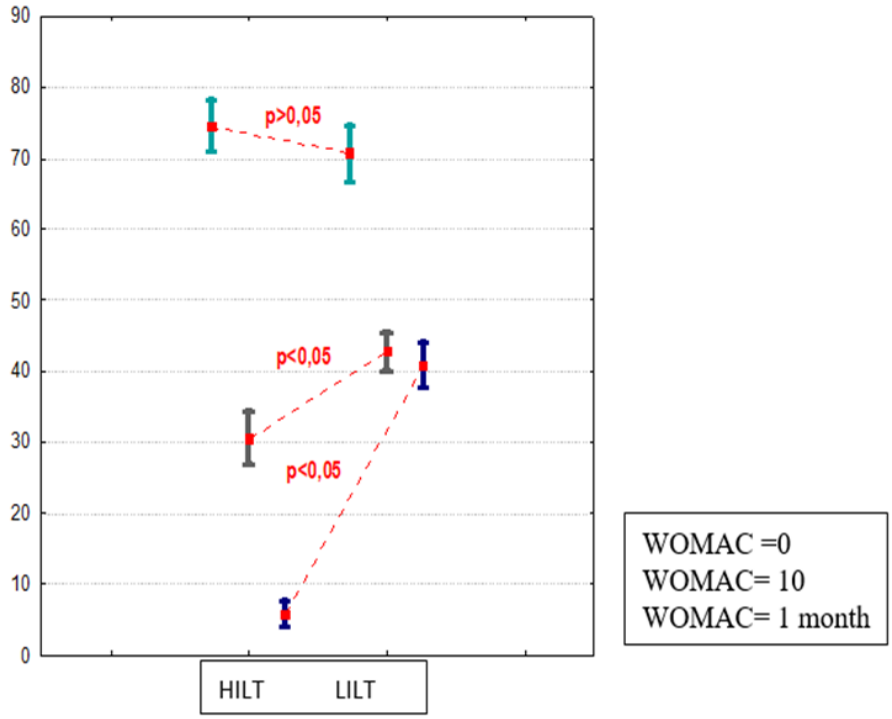


Figure 2: Comparison of WOMAC index between groups and within the group individually at three time points - 0, 10 days and 1 month

DISCUSSION

Our study revealed that both LILT and HILT treatments in patients with KOA led to reduced symptoms immediately after therapy and 1 month later. The observed result was more pronounced in patients treated with HILT laser.

Our results are similar to several other studies which used the same out-

come measure in patients with LILT treatment[15,16,17]. Several authors have confirmed the effectiveness of HILT therapy in reducing pain in different neurological and musculoskeletal disorders[18,19,20,21,22]. Specifically, studies investigated the effectiveness of HILT therapy in patients with KOA. Roheim MI *et al*. showed that HILT therapy was more effective than isolated exercising for reducing pain[23]. Siriratna *et al*. reported a more significant pain reduction measured with the WOMAC index in patients treated with HILT compared to the control group who received placebo24. The same conclusions were derived in a study published by Taher *et al*.[25].

In the last few years, studies have been published comparing the effectiveness of HILT and LILT 2[6, 27, 28]. Most of them showed positive results in the treatment of KOA. The studies were heterogeneous regarding study duration, number of controls, number of laser therapy sessions and outcome measures. For example, Vibisono *et al*. investigated the comparative effects of HILT and LLLT on leg balance in patients with KOA using the Berg Balance Scale (BBS) 26. Another study by Ahmad MA. *et al*. compared patients treated with LILT and exercise, and HILT and exercise for 12 weeks. Although both groups significantly improved regarding active knee flexion and Time Up and Go scores compared to baseline, the results were better in patients treated with HILT[27]. The double-blind randomized controlled trial by Astri SW. *et al*. also compared the outcome of treatment of patients randomized to LLLT and HILT. All patients received 6 sessions of laser therapy in combination with exercise therapy. After 6 sessions, both groups showed a significantly increased walking speed. Moreover, the improvement in pain and functional ability was faster and greater in the HILT group than in the LLLT group[28].

A more recent comparative study published by Bernadette *et al*. compared[27] subjects with KOS treated with HILT or LLLT. The recovery measured with the Knee Injury and Osteoarthritis Score (KOOS) was significantly better in the HILT patient ($p < 0.001$)[29].

In our study, the group of patients treated with HILT combined with exercises showed significantly better results in the Total WOMAC index compared to the group with LILT combined with exercises at the end of the study (evaluations were conducted at three time points: at 0-time, after 10-therapy sessions and after 1 month of treatment). This means that patients treated with HILT had a significant reduction in pain, significantly better physical function and less stiffness in the knee joints ($p=0.0001$). This is particularly important for the older population, which is also represented by a high percentage in the study (58.33%).

Our study supports the fact that HILT is a simple, non-invasive, and effective choice of treatment of patients with KOA.

Conclusion

Both LILT and HILT are effective physical modalities in reducing pain and promoting functional recovery in patients with KOA. HILT leads to significantly greater reduction in pain and stiffness, and improved physical function compared to patients with

KOA treated with LILT immediately after therapy and one month later. New high-quality studies are needed in the future involving larger patient samples and longer follow-up periods to further investigate the effects of HILT.

References

1. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. E Clinical Medicine. 2020; 29-30:100587. doi: 10.1016/j.eclinm.2020.100587
2. Shamsi S, Al-Shehri A, Al Amoudi KO, Khan S. Effectiveness of physiotherapy management in knee osteoarthritis: A systematic review. Indian Journal of Medical Specialities; 11(4):185-191.
3. Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. Braz J Phys Ther 2021; 25(2):135-146. DOI: 10.1016/j.bjpt.2020.08.004
4. Ferreira RM, Martins PN, Gonçalves RS. Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: An umbrella review 5-year update. Osteoarthr Cartil Open. 2024; 6(3):100497. doi: 10.1016/j.ocarto.2024.100497.
5. Alfredo PP, Johnson MI, Bjordal JM, Santos ATS, Peres GB, Junior WS, Casarotto RA. Efficacy of diadynamic currents as an adjunct to exercise to manage symptoms of knee osteoarthritis in adults: A randomized controlled clinical trial. Clin Rehabil. 2024;38(7):920-931. doi: 10.1177/02692155241236611.
6. Ahmad MA, A Hamid MS, Yusof A. Effects of low-level and high-intensity laser therapy as adjunctive to rehabilitation exercise on pain, stiffness and function in knee osteoarthritis: a systematic review and meta-analysis. Physiotherapy. 2022; 114:85-95.
7. Ganjeh S, Rezaeian ZS, Mostamand J. Low level laser therapy in knee osteoarthritis: A narrative review. Adv Ther. 2020;37(8):3433-3449. doi: 10.1007/s12325-020-01415-w.
8. Song HJ, Seo HJ, Kim D. Effectiveness of high-intensity laser therapy in the management of patients with knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. J Back Musculoskelet Rehabil. 2020;33(6):875-884. DOI: 10.3233/BMR-191738
9. Ray M. Laser therapy and osteoarthritis disability: An update of an unresolved topic. Nov Tech Arthritis Bone Res. 2017; 2(2): 555-585 DOI: 10.19080/NTAB.2017.02.555585
10. Ezzati K, Laakso EL, Salari A, Hasannejad A, Fekrazad R, Aris A. The beneficial effects of high-intensity laser therapy and co-interventions on musculoskeletal pain management: A systematic review. J Lasers Med Sci. 2020;11(1):81-90. DOI: 10.15171/jlms.2020.14
11. Akaltun MS, Altindag O, Turan N, Gursoy S, Gur A. Efficacy of high intensity laser therapy in knee osteoarthritis: a double-blind controlled randomized study. Clin Rheumatol. 2021;40(5):1989-1995. DOI: 10.1007/s10067-020-05469-7
12. Ekici B, Ordahan B. Evaluation of the effect of high-intensity laser therapy (HILT) on function,

muscle strength, range of motion, pain level, and femoral cartilage thickness in knee osteoarthritis: randomized controlled study. Lasers Med Sci. 2023;38(1):218. DOI: 10.1007/s10103-023-03887-y

13. Koevska V, Dimitrova-Nikolic E, Mitrevska B, Savevska-Gjerakaroska C, Gocevska M, Kalcovska B. Application of high-intensity laser in pain treatment of patients with knee osteoarthritis. Arch Pub Health 2021; 13 (2) 78-90. https://doi.org/10.3889/aph.2021.6008
14. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum. 2001;45(5):453-61 DOI: 10.1002/1529-0131(200110)45:5<453::aid-art365>3.0.co;2-w
15. Robbins SR, Alfredo PP, Junior WS, Marques AP. Low-level laser therapy and static stretching exercises for patients with knee osteoarthritis: A randomised controlled trial. Clin Rehabil. 2022; 36(2):204-213. DOI: 10.1177/02692155211047017
16. Huang Z, Chen J, Ma J, Shen B, Pei F, Kraus VB. Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015 Sep;23(9):1437-1444. doi: 10.1016/j.joca.2015.04.005.
17. Rayegani SM, Raeissadat SA, Heidari S, Moradi-Joo M. Safety and effectiveness of low-level laser therapy in patients with knee osteoarthritis: A systematic review and meta-analysis. J Lasers Med Sci. 2017 Summer;8(Suppl 1):S12-S19. doi: 10.15171/jlms.2017.s3.
18. Gocevska M, Nikolikj-Dimitrova E, Gjerakaroska-Savevska C. Effects of high - intensity laser in treatment of patients with chronic low back pain. Open Access Maced J Med Sci 2019;7(6):949-954. doi: 10.3889/oamjms.2019.117.
19. Choi HW, Lee J, Lee S, Choi J, Lee K, Kim BK, Kim GJ. Effects of high intensity laser therapy on pain and function of patients with chronic back pain. J Phys Ther Sci. 2017;29(6):1079-1081 DOI: 10.1589/jpts.29.1079
20. Atan T, Bahar-Ozdemir Y. Efficacy of high-intensity laser therapy in patients with adhesive capsulitis: a sham-controlled randomized controlled trial. Lasers Med Sci 2021; 36(1):207–217. DOI: 10.1007/s10103-020-03121-z
21. Chen Y-W, Cheng Y-Y, Lee Y, Chang S-T, The immediate effect of high-intensity laser therapy on pain relief and shoulder function in patients with subacromial impingement syndrome. World J Phys Rehabil Med 2020; 4(1):1016.
22. Kaydok E, Ordahan B, Solum S, Karahan AY. Short-term efficacy comparison of high-intensity and low intensity laser therapy in the treatment of lateral epicondylitis: a randomized double-blind clinical study. Arch Rheumatol 2019; 35(1):60–67. DOI: 10.5606/ArchRheumatol.2020.7347
23. Roheym M.I, Morsy, M.E. Saber, M. Balbaa, A.A.Hegazy, S.M. Impact of high-power laser therapy on bilateral kneeosteoarthritis: A randomized trial. Fizjoterapia Pol 2023; 23: 162–168.
24. Siriratna P, Ratanasuti C, Manissorn T, Santiniyom N, Chira-

Adisai W. Short-term efficacy of high-intensity lasertherapy in alleviating pain in patients with knee osteoarthritis: A single-blind randomised controlled trial. Pain Res Manag 2022, 1319165. DOI: 10.1155/2022/1319165

25. Taheri P, Maghroori R, Aghaei M. Effectiveness of high-intensity laser therapy for pain and function in knee osteoarthritis: A randomized controlled trial. Middle East J Rehabil Health Stud 2024; 11, e134330.

26. Wibisono K, Handoyo R, Setiawati E. Comparison of the effectiveness of high intensity laser therapy (HILT) and low-level laser therapy (LLLT) on improving balance in knee osteoarthritis. Medica Hospitalia J Clin Med 2024;11(1):33. DOI: 10.36408/mhjcm.v11i1.984

27. Ahmad MA, Moganan M, A Hamid MS, Sulaiman N, Moorthy U, Hasnan N, Yusof A. Comparison between low-level and high-intensity laser therapy as an adjunctive treatment for knee osteoarthritis: A randomized, double-blind clinical trial. Life (Basel). 2023;13(7):1519. doi: 10.3390/life13071519.

28. Astri SW, Murdhana N, Nusdwinuringtyas N, Kekalih A, Sunarjo P, Soewito F. The comparison of the low-level laser therapy and high intensity laser therapy on pain and functional ability in knee osteoarthritis. J Indon Med Assoc 2023; 72(6) https://doi.org/10.47830/jinma-vol.72.6-2022-826

29. Natalia BR, Widagda IM, Julianti HP. Comparison of the Effectiveness of High Intensity Laser therapy (HILT) and Low-Level Laser Therapy (LLLT) on Functional Improvement in Knee Osteoarthritis Patients. Medica Hospitalia: Journal of Clinical Medicine. 2024 Jul 31;11(2):132-7. DOI:10.36408/mhjcm.v11i2.967

ORAL HEALTH

ANALYSIS OF PERIAPICAL PROCESSES AND BONE LOSS WITH 2D AND 3D RADIOLOGICAL DIAGNOSTICS

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Key words: 3D CBCT, panoramic scan, two-dimensional scan, three-dimensional scan, bone loss

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Abstract

In recent years, dental practice has increasingly given preference to three-dimensional versus two-dimensional X-ray diagnostics. The three-dimensional view in layers (sections) and the use of modern software allow for an incomparably better visualization of a patient's oral cavity status compared to conventional orthopantomographic X-ray devices. Objective: The main objective of this study was to identify the difference between three-dimensional and two-dimensional radiological diagnostics and to demonstrate the advantages of 3D X-ray by presenting several clinical cases. Bone loss, as well as the presence of periapical processes and their actual size were analyzed, and the parameters were compared on two-dimensional and three-dimensional images. Materials and method: The examination took place at the 3D-RDG (Dental X-ray Diagnostics 3D-RTG Dental Imaging Skopje) Center in Skopje. To achieve the set goal, we made a radiological comparison of two-dimensional and three-dimensional X-ray images in 73 subjects, of which 40 (54.79%) teeth in the upper jaw and 33 (45.21%) teeth in the lower jaw. All subjects were scanned with the same X-ray device - Green X, which is from the latest generation of X-ray devices, with a minimum dose of radioactive radiation - 2.9 sec. for 3D-CBCT and 3.9 sec. for panoramic imaging. For detailed analysis and diagnosis of the cases, the most modern and sophisticated software, EzDent-i and Ez3D-i, were used, offering various fields of view projections. Results: Of the 73 analyzed teeth, a periapical process was diagnosed in 52.05% of teeth using 2D and in all teeth using 3D. The actual size of the periapical process was significantly larger on three-dimensional radiography compared to two-dimensional radiography ($p<0.0001$). Bone loss on 3D was recorded in 50% of maxillary teeth and in 33% of mandibular teeth. Conclusion: Three-dimensional radiography provides much clearer diagnostic values in the diagnosis of periapical changes compared to two-dimensional images. Three-dimensional radiography provides clearer results in terms of the actual size of periapical changes. Bone loss can be reliably diagnosed only with three-dimensional radiography, and is more common in the upper jaw.

ОРАЛНО ЗДРАВЈЕ

АНАЛИЗА НА ПЕРИАПИКАЛНИ ПРОЦЕСИ И КОСКЕН ГУБИТОК СО 2D И 3D РАДИОЛОШКА ДИЈАГНОСТИКА

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Клучни зборови: 3D CBCT, панорамска снимка, дводимензионална снимка, тридимензионална снимка, коскен губиток

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Печатарски права: ©2025. Марина Ефтимоска, Марио Јурхар, Василка Ренџова, Емилија Стефановска, Стевица Ристовска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Во последните години од стоматолошката практитка, сè повеќе се дава предност на тридимензионалната наспроти дводимензионалната РДГ дијагностика. Тридимензионалниот приказ по слоеви, односно пресеци, и примената на современиот софтвер, овозможува неспоредливо подобра визуелизација на статусот во оралната празнина на пациентот, за разлика од конвенционалните ортопантомографски РДГ апарати. Главна цел на овој труд беше да се воочи разликата помеѓу тридимензионалната и дводимензионалната радиолошка дијагностика и да се докаже предноста на 3D РДГ, преку приказ на повеќе клинички случаи. Беше анализиран коскен губиток како и присуство на периапикални процеси и нивната реална големина, а параметрите беа компарирани на дводимензионална и на тродимензионална снимка. Материјали и методи: Испитувањето се одвиваше во 3D-RDG (Рендген-дијагностика за заби 3Д-РТГ Дентал Имицинг Скопје), центарот во Скопје. За реализација на поставената цел направивме радиолошка споредба на дводимензионална и тридимензионална РДГ снимка кај 73 испитаници, од кои 40 (54.79%) заби во горна вилица и 33 (45.21%) заби во долна вилица. Сите испитаници беа снимани со ист РДГ апарат - Green X, кој е од последната генерација РДГ апарати, со минимална доза на радиоактивно зрачење, и тоа 2.9 сек. за 3D-CBCT и 3.9 сек. за панорамска снимка. За детална анализа и дијагноза на случаите се применуваа најсовремени и софистицирани софтвери, EzDent-i и Ez3D-i, кои овозможуваат различни проекции на видното поле. Резултати: Од анализираните 73 заби, периапикален процес беше дијагностициран кај 52.05% од забите на 2D и кај сите заби на 3D. Реалната големина на периапикалниот процес беше сигнификантно поголема на тридимензионалната рендгенографија, споредено со дводимензионалната рендгенографија ($p<0.0001$). Коскен губиток на 3D беше регистриран кај 50% од забите во горната вилица и кај 33% од забите во долната вилица. Заклучок: Тридимензионалната рендгенографија дава многу појасни дијагностички вредности при дијагноза на периапикалните промени за разлика од дводимензионалните снимки. Појасни резултати во однос на реалната големина на периапикалните промени дава тридимензионалната рендгенографија. Коскениот губиток со сигурност може да се дијагностицира само на тридимензионална рендгенографија, а тој се среќава почесто во горната вилица

Introduction

Apical periodontitis represents the primary alteration linked to infection within the root canal's microbial environment.

The accepted reference standard for radiological detection of a periapical process is the periapical radiograph. In the early stages of apical periodontitis, bone resorption may be minimal or covered by other anatomical-morphological structures. Cone-beam computed tomography (CBCT), as an additional or primary diagnostic aid, allows detection of the same change even before it becomes visible on a conventional periapical radiograph, that is, in the early stage. Patel et al.[1] and Pineda[2] in their research found that diagnosing with the sensitivity of the CBCT beam is 34-54.2% higher compared to intraoral radiography for detecting periapical changes. Dutra[3] in his study emphasized that the highest precision in diagnosing periapical changes was achieved with CBCT. The difference between a nasopalatine cyst and a periapical process was explored by Faitaroni4, who pointed out that CBCT provided a detailed, high-resolution image that helped in establishing the initial diagnosis and therapy planning. However, histopathological analysis is essential in the differential diagnosis. In a long-term study, Sharma[5] concluded that the healing process of the tooth was significantly better with the use of CBCT due to the initial precise diagnosis, which was substantially higher compared to conventional retroalveolar radiographs.

Maillet[6] examined the correlation between infected canals in upper molars and maxillary sinusitis. In his study, he made a distinction between two-dimensional and three-dimensional diagnostics and demonstrated that the sensitivity of the CBCT beam was 50% greater than that of retroalveolar radiographs. Of 135 cases examined, 98 maxillary sinusitis cases were caused by dental issues, while 37 were of non-odontogenic origin. Cone-beam computed tomography was proven to be the best diagnostic aid, as shown in Low's study[7], which focused on the overall pathology of teeth, root canal filling revisions, expansion of the periapical process toward the maxillary sinuses, thinning, and erosion of the sinus floor, untreated canals, etc. Burgos[8] suggests that presenting the benefits and capabilities of CBCT for precise diagnostics through videos can help patients agree to this type of imaging at the start of treatment (research in the U.S. Army). Cui[9] in his study emphasized that the combination of conventional radiography and CBCT provided significantly better results in endodontic therapy over a longer period. Songa[10] aimed to demonstrate the advantages of CBCT in his case of a 21-year-old patient with expansion of a periapical process in the lower first molar and affected furcation. The distal root of this tooth had bone resorption only on the lingual side. This diagnostic precision would not have been possible with a two-dimensional radiograph.

In her 5-year study, Ritika[11] stated that with the help of cone-beam computed tomography, compared to 2D radiographs, periapical changes can be more accurately monitored during their healing. A similar interpretation has been provided by Tom[12]. In his research, he highlighted that 2D did not provide an accurate image in terms of the actual size of the peri-

apical changes. Cone-beam computed tomography is recommended as the sole method for the precise diagnosis of osseous defects, which occur more frequently on the labial/buccal side, compared to the palatal/lingual side[13]. This was confirmed by Bayat[14] in his study. Through his cases, CBCT has proven to be superior compared to 2D radiographs when it comes to the involvement of bone defects. The amount of bone tissue loss, whether horizontal or vertical, can only be diagnosed and determined with 3D CBCT[15]. Assiri[16] points out that CBCT is the most precise of all radiographic methods for diagnosing periapical lesions, osseous defects, and furcation involvement.

The main goal of this paper was to highlight the difference between three-dimensional and two-dimensional radiological diagnostics and to demonstrate the advantages of 3D X-rays by presenting multiple clinical cases. Bone loss, as well as the presence of periapical processes and their actual size were analyzed, and the parameters were compared between two-dimensional and three-dimensional imaging.

Materials and methods

In our study, to achieve the set goal, a Green X X-ray machine from the latest generation was used, with a minimal dose of radioactive radiation, specifically 2.9 seconds for 3D-CBCT and 3.9 seconds for panoramic imaging.

X-ray machines of this generation represent a 4-in-1 system and have the capability to take four types of images:

1. Cone-beam computed tomography (CBCT) with different fields of view (FOV)
2. Cephalometric scan
3. Two-dimensional digital panoramic (half panorama, left or right, two-dimensional projection of the TMJ, as well as maxillary sinuses)
4. Model scan - with the further possibility of adapting the model to a patient's 3D image, in order to create implant guides.

The study was conducted at the 3D-RDG (Radiology Diagnostics for Teeth) Center in Skopje (a branch of PHI-Polyclinic Secondary Level EDG-2 Gevgelija).

The segmented, full 3D-CBCT images, as well as the orthopantomogram, were taken using the Green X digital X-ray machine.

For detailed analysis and diagnosis of the cases, the most modern and sophisticated software, EzDent-i and Ez3D-i, were used, which offered various projections of the visible field.

Tests were conducted on 73 teeth, of which 40 (54.79%) were in the upper jaw and 33 (45.21%) in the lower jaw. The anatomical-morphological characteristics of the teeth and their pathologies were analyzed on 2D and 3D X-rays (two-dimensional and three-dimensional radiography).

3D - CBCT full and segmented image procedure

The patient enters the X-ray room and stands upright, with the head stabilized and aligned to the facial midline. The therapist leaves and closes the door of the X-ray room, pressing the button to start the exposure in a duration of 2.9 seconds. After the image is taken, the patient is released from the X-ray machine.

2D - Panoramic image procedure

The patient enters the X-ray room and stands upright, with the head stabilized and aligned to the facial midline, the Frankfurt plane, and the canine line. The therapist leaves and closes the door of the X-ray room, pressing the button to start the exposure in a duration of 3.9 seconds. After the image is taken, the patient is released from the X-ray machine. After the images are taken, a so-called 3D *versus* 2D analysis is performed, where radiographic signs from both images are compared.



Image 1: Positioning of the patient - canine line, interincisal line, and the line corresponding to the Frankfurt plane

Endo – software

Preoperative segmented imaging with a 4x4 field of view represents an excellent diagnostic method in the treatment of teeth from an endodontic perspective. The voxel size in the resolution of this image is 0.49 micrometers.

The sophisticated software and the "endo mode" tool allow for a 360-degree rotation around the tooth, marking of the root canals, determination of periapical lesions, differential diagnostic separation of root fractures or lateral canals, determination of the exact root morphology, and working length of the canals. With marked canals, the therapist immediately knows how to proceed, i.e., through a treatment plan, to minimally invasively treat the tooth from an endodontic perspective. After the images were taken, we proceeded to a so-called 3D *versus* 2D analysis, in which radiographic signs were compared from both perspectives.

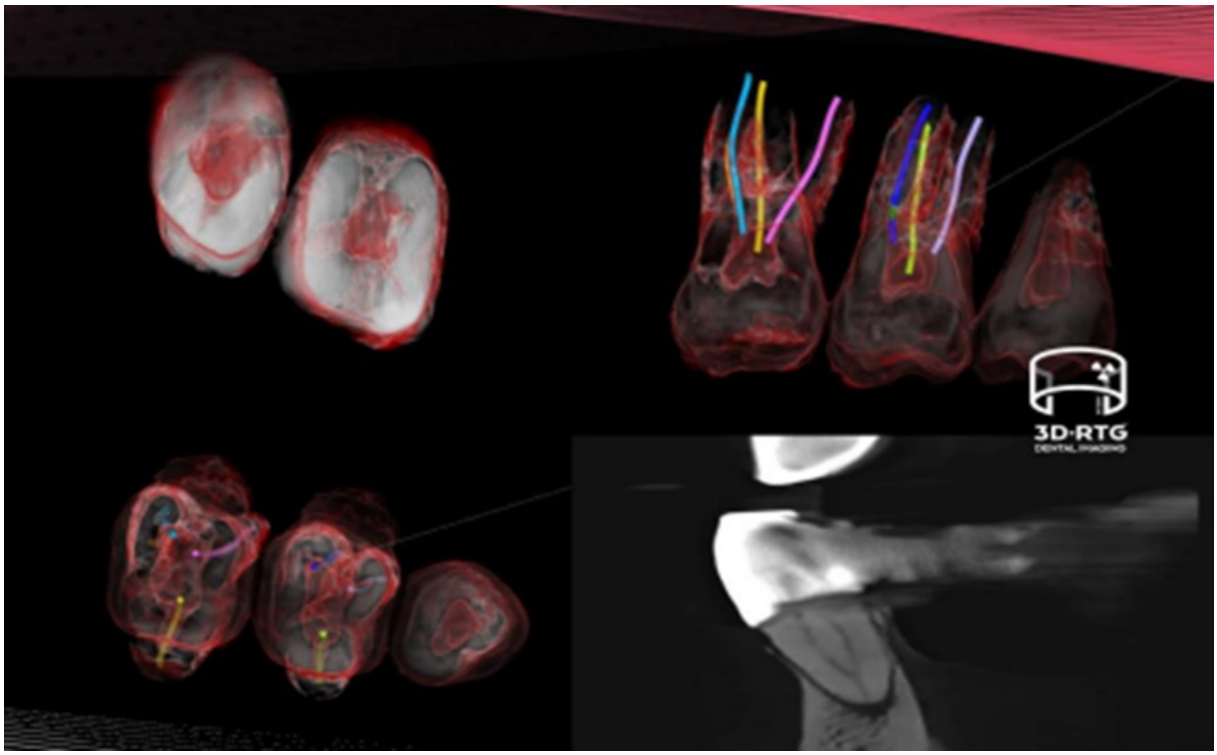


Image 2: Endo-mode – as part of the sophisticated Ez3D-i software. The corresponding tooth structures are marked with color that is updated according to the tissue density. The canals of the relevant teeth are also outlined.

Results:

In this study, 73 teeth were analyzed, of which 40 (54.79%) were in the upper jaw and 33 (45.21%) were in the lower jaw (Table 1).

Table 1: Distribution of teeth from the upper and lower jaws

Jaw	n (%)
Upper	40 (54.79)
Lower	33 (45.21)

The anatomical and morphological characteristics of the teeth and their pathologies were analyzed using 2D and 3D.

A periapical process was diagnosed in 38 (52.05%) teeth using 2D and in all teeth using 3D (Table 2, Figure 1).

The proportion of teeth with a periapical process on 2D was 38/73 = 0.521 or 52.1%. The proportion of teeth with a periapical process on 3D was 73/73 = 1 or 100%. The difference in the proportion of teeth with a periapical process detected on two-dimensional and three-dimensional radiography was statistically significant, with $p < 0.0001$, and was significantly higher on 3D (Table 2, Figure 1).

Table 2: Presence of periapical process – 2D *versus* 3D

Periapical process	RTG	
	2D n (%)	3D n (%)
yes	38 (52.05)	73(100)
no	35(47.95)	0

McNemar test p<0.00000

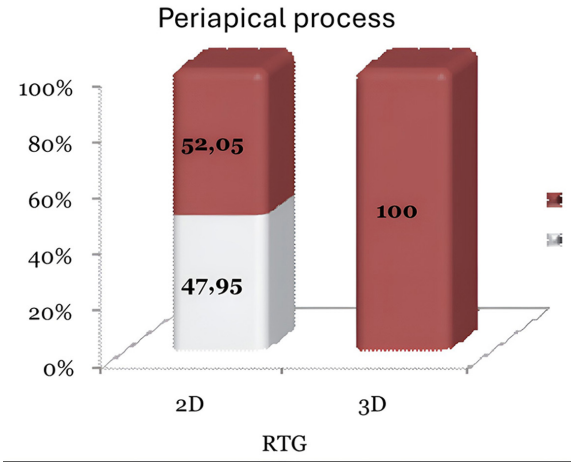


Figure 1: Illustration of periapical process findings on 2D and 3D

The average size of the periapical process on 2D was 1.7±0.6 mm (Table 3, Figure 2). Half of the teeth showed periapical lesions larger than 1.75 mm (Table 3).

Table 3: Presence of periapical process – 2D *versus* 3D

Actual size of the periapical process 2D	Statistical parameter
n	38
mean ± SD	1.69 ± 0.6
min- max	0.5 – 3.0
median (IQR)	1.75 (1 – 2)

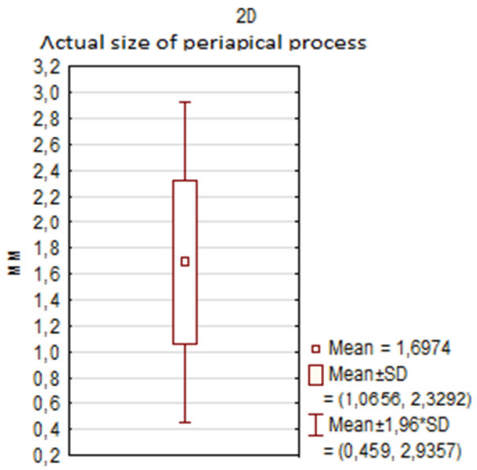


Figure 2: actual size of the periapical process – 2D

The average size of the periapical process on 3D was 3.6±1.4 mm, while half of the teeth showed periapical lesions larger than 3 mm (Table 4, Figure 3).

Table 4: Presence of periapical process – 2D *versus* 3D

Actual size of the periapical process – 3D	Statistical parameter
n	73
mean ± SD	3.59 ± 1.4
min- max	1.5 – 8
median (IQR)	3 (2.5 – 4)

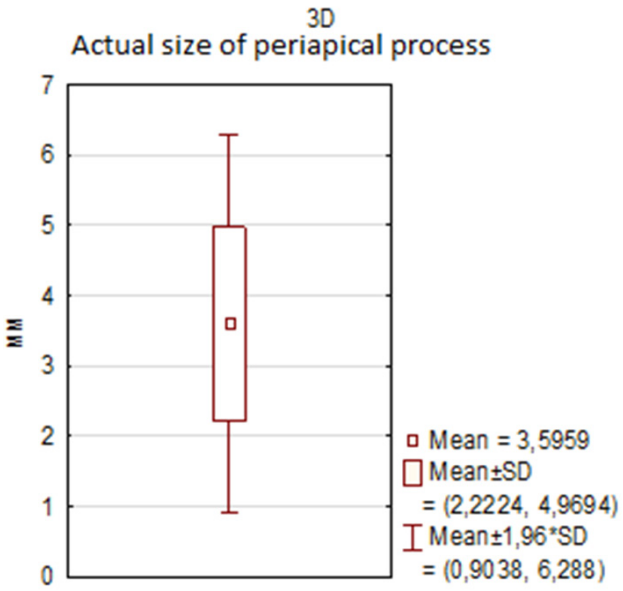


Figure 3: actual size of the periapical process 3D

The actual size of the periapical process was significantly larger on three-dimensional radiography compared to two-dimensional radiography (p<0.0001). The average size of the periapical process was 1.7 ± 0.6 mm on 2D and 4.35 ± 1.3 mm on 3D (Table 5, Figure 4).

Table 5: Comparison of the actual size of the periapical process – 2D *versus* 3D

Radiography	Statistical parameter		p-level
	n	mean ± SD	
Actual size of the periapical process 2D		1.69 ± 0.6	t=16.05 ***p=0.000000
Actual size of the periapical process 3D	38	4.35 ± 1.3	

t (Student t-test)
***sig p<0.0001

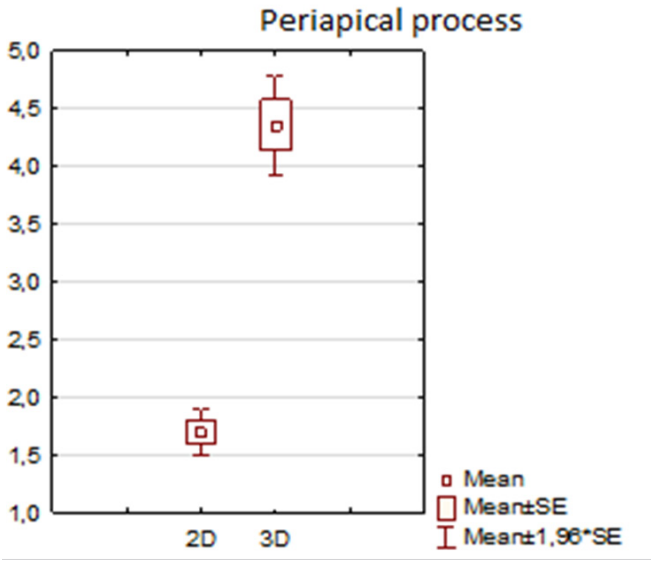


Figure 4: Illustration of the actual size of the periapical process – 2D *versus* 3D

2D radiography did not present bone loss in any tooth, while 3D X-ray diagnosed bone loss in 31 (42.47%) teeth. The difference in the proportion of teeth with bone loss, depending on the radiographic technology, was statistically significant ($p<0.000001$).

3D radiography significantly more frequently detected bone loss compared to 2D (Table 6, Figure 5).

Table 6: Bone loss – 2D *versus* 3D

Bone loss	Radiography	
	2D	3D
Yes	0	31 (42.47%)
No	73 (100%)	42 (57.53%)

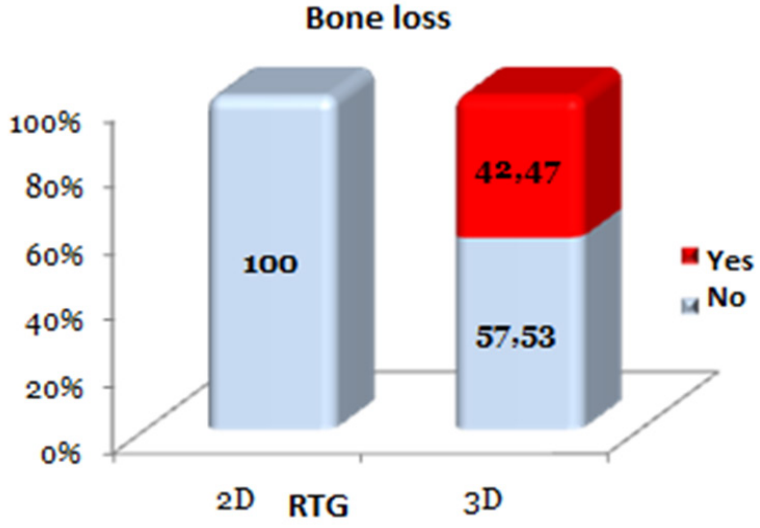


Figure 5: Illustration of bone loss on 2D and 3D

3D registered bone loss in 20 (50%) teeth from the upper jaw and in 11 (33.33%) teeth from the lower jaw. The difference in the prevalence of bone loss, depending on the location of the teeth in the upper or lower jaw, was not statistically significant, but it was more common in the upper jaw (0.15) (Table 7, Figure 6).

Table 7: Bone loss in teeth from the upper and lower jaw

Radiography	Jaw			p-level
	n	upper n (%)	lower n (%)	
Yes	31	20 (50)	11 (33.33)	X^2=2.0 p=0.15
No	42	20 (50)	22 (66.67)	

X^2(Pearson Chi-square)

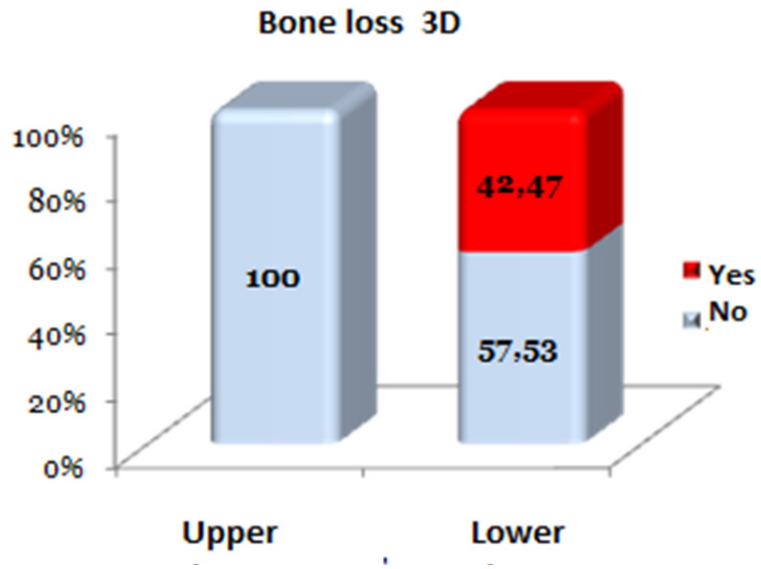


Figure 6: Illustration of bone loss on 3D in the upper and lower jaw expressed in %

Discussion

In the past decade, the question of whether patients need to undergo three-dimensional radiography has been increasingly discussed in dental practice.

Dentists debate over this question due to concerns that patients would be exposed to a higher dose of radioactive radiation.

With the innovation of digital radiography, radioactive radiation has been minimized.

A new trend involves CBCT (Cone Beam Computed Tomography) devices of the green generation (Green CT) and imaging according to the ALARA principle.

1Sv (Sievert) is a unit of measurement for the absorbed dose of radioactive radiation.

This radiation dose is high and is considered to potentially cause pathological changes (undesired cell division) in the tissues of patients.

Panoramic radiographs and three-dimensional radiography are characterized by radioactive radiation ranging from 15 to 30 microsieverts.

One Sievert (Sv) is equivalent to 1,000,000 microsieverts, meaning the pathological threshold is far beyond the point where it could be questioned whether the imaging is dangerous for the patient's health. Smart devices from the green generation are characterized by an even smaller dose of radioactive radiation (less than 15 microsieverts).

Through sophisticated software, by entering patient details, radiographic devices automatically adjust the radioactive dose based on bone density, which changes over the years. This ensures that patients absorb the minimum dose necessary to accurately image the anatomical and morphological structures of interest.

As the device produces the beam and it penetrates into patient tissues, the device loses its power and fades until the therapist enters the radiography room to release the patient from the device. This fact indicates that radiography is safe for the therapist and all clinical staff involved in radiographic diagnostics. Considering these improvements, radiography today can be considered a completely safe method for top-notch diagnostics and flawless therapy for patients. Three-dimensional versus two-dimensional radiographic diagnostics represents a current and interesting comparison regarding therapy outcomes in dental practice. We are increasingly turning to the use of 3D CBCT for initial and accurate diagnosis. This represents a new trend and ergonomic principle in dental treatment.

The therapist is immediately familiar with the complete image of the area of interest and is prepared to proceed with accurate therapy. This method enables therapists to protect patients from ineffective therapy and reduce the amount of time patients spent in the dental chair.

The significantly higher accuracy of three-dimensional radiography is also demonstrated by comparing voxels and pixels. The fact that the resolution of the three-dimensional image is measured in voxels, which are characterized by the same size in all directions, points to the greater diagnostic value compared to pixels in two-dimensional radiographs, where only height and length are characteristic.

Periapical Changes

From the 73 teeth analyzed in this study, a periapical process was diagnosed in 38 (52.05%) teeth on 2D and in all teeth on 3D.

The proportion of teeth with a periapical process on 2D was 38/73 = 0.521 or 52.1%. The proportion of teeth with a periapical process on 3D was 73/73 = 1 or 100%. The difference in the proportion of teeth with a periapical process detected on two-dimensional and three-dimensional radiography was statistically significant, with $p < 0.0001$, and was significantly greater on 3D.

(Table 2, Figure 1)

Similar results were presented by Patel1, who stated that periapical changes could be diagnosed with CBCT even before they became visible on a conventional two-dimensional image, in the early stage.

On the other hand, Pineda et al.2 in his research found that the diagnosis using the sensitivity of the CBCT beam was by 34-54.2% more accurate compared to two-dimensional imaging for detecting periapical changes.

Patil et al.15 pointed out that periapical changes, which could not be seen on 2D, were visible on 3D. This study included 178 teeth, of which a periapical process was observed in 31.5% on 2D and 52.2% on CBCT.

The average size of the periapical process on 2D was 1.7 ± 0.6 mm (Table 3, Figure 2).

The average size of the periapical process on 3D was 4.35 ± 1.3 mm (Table 4, Figure 3).

The actual size of the periapical process was significantly larger on three-dimensional radiography compared to two-dimensional radiography ($p < 0.0001$) (Table 5, Figure 4).

These results are similar to those presented by Ordinola-Zapata17, who stated that the volume of periapical changes in endodontically treated and untreated teeth could only be monitored with 3D CBCT. Two-dimensional radiography does not have this capability.

Unlike all other radiographic methods, CBCT is characterized by the highest sensitivity regarding periodontal defects18.

Fernanda19 emphasized that diagnostics based on 2D for determining the exact size of periapical changes is limited and should not be used for scientific research.

Osseous Defects

2D radiography did not show bone loss in any tooth, whereas 3D CBCT diagnosed bone loss in 31 (42.47%) teeth. The difference in the proportion of teeth with bone loss, depending on the radiographic technology, was statistically significant ($p < 0.000001$) (Table 6, Figure 5).

3D radiography significantly more frequently detected bone loss compared to 2D. Bone loss on 3D was registered in 20 (50%) teeth from the upper jaw and in 11 (33.33%) teeth from the lower jaw. The difference in the prevalence of bone loss, based on the location of the teeth in the upper or lower jaw, was not statistically significant, but it was more common in the upper jaw (0.15) (Table 7, Figure 6).

Gambarini20 underscores that preoperative CBCT accurately diagnoses whether there is fenestration or not. According to Urbani's study21, fenestrations are more common in the maxilla compared to the mandible. Cone-beam computed tomography is recommended as the only method for the precise diagnosis of osseous defects. These defects occur more frequently on the labial/buccal side, compared to the palatal/lingual side13.

Conclusions

Based on the results obtained in this study, the following conclusions can be drawn:

1. The comparative two-dimensional *versus* three-dimensional radiographic analysis, in relation to the presence of periapical processes, showed that three-di-

mensional radiography provided much clearer diagnostic values compared to two-dimensional images when diagnosing periapical changes.

2. When analyzing and diagnosing the actual size of periapical changes, the size was significantly larger on 3D. Therefore, three-dimensional radiography provides clearer results in relation to the actual size of periapical changes.
3. When analyzing radiographic images of the same teeth and comparing 2D and 3D images, a statistically significant difference was found regarding bone loss from the alveolar ridges; bone loss was detected using 3D, while no cases were seen using 2D. We can conclude that bone loss can certainly be diagnosed only with three-dimensional radiography.
4. Three-dimensional radiography revealed that bone loss was more frequently observed in the upper jaw than in the lower jaw from the analyzed teeth, Bone loss was more common in the upper jaw due to the spongy tissue of the maxillary alveolar ridge, as opposed to the compact portion of the mandibular alveolar ridge.

In general, it can be concluded that the limitations that arise when diagnosing with two-dimensional radiography are not present in 3D. Exposure to additional radiographic radiation is avoided by using 3D CBCT as an initial image, leaving behind two-dimensional projections.

With modern digital three-dimensional radiographic diagnostics, we achieve the highest diagnostic values, minimal exposure of patients to radioactive radiation, and high-quality and well-planned endodontic therapy.

References

1. Patel S, Dawood A, Mannocci F, Wilson R, Pitt Ford T. Detection of periapical bone defects in human jaws using cone beam computed tomography and intraoral radiography. Int Endod J. 2009;42(6):507–15.
2. Pineda F. Roentgenographic investigation of the mesiobuccal root of the maxillary first molar. Oral Surg Oral Med Oral Pathol. 1973;36(2):253–60.
3. Dutra KL, Haas L, Porporatti AL, et al. Diagnostic accuracy of cone-beam computed tomography and conventional radiography on apical periodontitis: A systematic review and meta-analysis. J Endod 2016;42(3):356-364.
4. Faitaroni LA, Bueno MR, Carvalhosa AA, et al. Differential diagnosis of apical periodontitis and nasopalatine duct cyst. J Endod 2011;37(3):403-410.
5. Sharma G, Abraham D, Gupta A, et al. Comparison of healing assessments of periapical endodontic surgery using conventional radiography and cone-beam computed tomography: A systematic review. Dentomaxillofac Radiol 2017;46(7):20170210. doi:10.1259/dmfr.20170210.
6. Maillet M, Bowles WR, McClanahan SL, et al. Cone-beam computed tomography evaluation of maxillary sinusitis. J Endod 2011;37(6):753-757. doi:10.1016/j.joen.2011.02.032.

7. Low KM, Dula K, Burgin W, von Arx T. Comparison of periapical radiography and limited cone beam tomography in posterior maxillary teeth referred for apical surgery. J Endod. 2008;34(5):557–62

8. Burgos K, Dutner JM, Phillips MB. Assessment of perceptions of cone-beam computed tomography and endodontic treatment in a military population. J Endod 2021;47(7):1087-1091. doi:10.1016/j.joen.2021.04.020.

9. Cui JJ, Peng B, Lin W. Effects of combining CBCT technology with visual root canal recurrence in treatment of elderly patients with dental pulp disease. J Endod 2017;21(5):903-907.

10. Songa VM, Jampani ND, Babu Venkateshwara, Buggapati L, Mittapally S. Accuracy of Cone Beam Computed Tomography in Diagnosis and Treatment Planning of periodontal Bone Defects: A Case Report. J Clin Diagn Res. 2014;8(12):ZD23-ZD25.

11. Dhamija R, Tewari S, Gupta A. Two- and three-dimensional healing assessment after endodontic microsurgery in through-and-through periapical lesions: 5-year follow-up from a randomized controlled trial. Int Endod J 2024 May 17. doi:10.1111/iej.14084.

12. Schloss T, Sonntag D, Kohli MR, Setzer FC. Comparison of 2- and 3-dimensional healing assessment after endodontic surgery using cone-beam computed tomographic volumes or periapical radiographs. J Endod 2017;43(7):1072-1079. doi:10.1016/j.joen.2017.02.007.

13. Pan HY, Yang H, Zhang R, et al. Use of cone-beam computed tomography to evaluate the prevalence of root fenestration in a Chinese subpopulation. Int Endod J 2014;47(11):1072-1078. doi:10.1111/iej.12117.

14. Bayat S, Talaeipour AR, Sarlati F. Detection of simulated periodontal defects using cone-beam CT and digital intraoral radiography. Dentomaxillofac Radiol 2016;45(7):20160030. doi:10.1259/dmfr.20160030.

15. Patil BA, Shakeel S. Evaluation of endo-perio lesions using cone beam computed tomography (CBCT): A cross-sectional study. J Clin Periodontol 2023 Oct 24;7:235-243. doi:10.11607/prd.6380.

16. Assiri H, Dawasaz AA, Alahmari A, Asiri Z. Cone beam computed tomography (CBCT) in periodontal diseases: A systematic review based on the efficacy model. BMC Oral Health 2020 Jul 8;20(1):191. doi:10.1186/s12903-020-01106-6.

17. Ordinola-Zapata R, Bramante CM, Duarte MH, et al. The influence of cone-beam computed tomography and periapical radiographic evaluation on the assessment of periapical bone destruction in dog's teeth. Oral Surg Oral Med Oral Pathol Oral Radiol 2011;112(2):272-279. doi:10.1016/j.tripleo.2011.01.031.

18. Bagis N, Kolsuz ME, Kursun S, Orhan K. Comparison of intraoral radiography and cone-beam computed tomography for the detection of periodontal defects: An in vitro study. BMC Oral Health 2015; 15: 64.

19. Ullmann López F, Poli Kopper PM, Cucco C, et al. Accuracy of cone-beam computed tomography and periapical radiography

in apical periodontitis diagnosis. J Endod 2014;40(12):2057-2060. doi:10.1016/j.joen.2014.09.003.

20. Gambarini G, Miccoli G, Gaimari G, et al. Detection of bone defects using CBCT exam in an Italian population. J Endod 2017;43(8):7523848. doi:10.1155/2017/7523848.

21. Urbani G, Lombardo G, Filippini P, Nocini FP. Dehiscence and fenestration: Study of distribution and incidence in a homogeneous population model. SM 1991;11(2):113-118. PMID:1925766.

ORAL HEALTH

TITRATABLE ACIDITY AND PH OF COMMERCIAL MOUTHWASHES: A COMPREHENSIVE ANALYSIS

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Key words: mouthwashes, pH, titratable acidity, buffering capacity

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Competing Interests: The author have declared that no competing interests

Abstract

The aim of this study was to measure and analyze the pH and titratable acidity (TA) of a wide range of commercial mouthwashes available in the Republic of North Macedonia, and to assess their potential erosive effects. Material and methods: A comprehensive market analysis was performed in the Republic of North Macedonia, including traditional markets (pharmacies, cosmetic chains, and consumer goods markets) as well as the online market. One to three packs of each mouthwash were purchased directly from vendors according to the inclusion and exclusion criteria, without requesting free samples from manufacturers or importers. A total of 81 mouthwashes were analyzed. pH and TA measurements were performed twice for each mouthwash, with results presented as Mean±SD. Results: The mean pH of the mouthwashes was 5.28±0.98 (range: 3.24 -7.74). More than half (n=48, 59.3%) had pH values below the critical threshold of 5.5. Only four (4.9%) had an initial pH ≥7. To neutralize acidic mouthwashes, an average of 5.75±10.29 ml of 0.1M NaOH was required (range: 0.01–81.20 ml). TA ranged from 0.01 to 162.4 mmol/l, with a mean of 11.50±20.58 mmol/l. Conclusion: A significant proportion of the mouthwashes (59.3%) had pH values below the critical threshold of 5.5. The titratable acidity values varied widely, with some mouthwashes exhibiting extremely high TA levels. Further research is needed to establish clear guidelines for safe use of mouthwashes with respect to their pH and titratable acidity values, especially to show the association between pH and TA of mouthwashes and the buffer capacity of saliva.

ОРАЛНО ЗДРАВЈЕ

ТИТРАЦИСКАТА КИСЕЛОСТ И РН НА КОМЕРЦИЈАЛНИ ВОДИЧКИ ЗА ПЛАКНЕЊЕ НА УСТА: ДЕТАЛНА АНАЛИЗА

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Клучни зборови: водички за плакнење на уста, рН, титрациска киселост, пуферски капацитет.

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Печатарски права: ©2025. Марија Андоновска, Влатко Коколански, Спиро Спасовски, Бојан Попоски, Ќиро Ивановски, Јулијана Николовска, Олга Гигопулу. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа оригиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Целта на оваа студија беше да се измери и анализира рН и титрациската киселост (ТК) на широк спектар на комерцијални водички за плакнење на устата, достапни во Република Северна Македонија, за да се процени нивниот потенцијален ерозивен ефект. Материјал и методи: Беше спроведена анализа на пазарот на Република Северна Македонија, вклучувајќи ги традиционалните пазари (аптеки, козметички ланци и маркети), како и онлајн пазарот. Беа купени 1 до 3 примероци од секоја водичка за плакнење на устата директно од продавачите, согласно критериумите за вклучување во и исклучување од студијата, без барање бесплатни примероци од производувачите или увозниците. Беше анализирана вкупно 81 водичка за плакнење на устата. Мерењата на рН и ТК беа изведени двапати за секоја водичка, а резултатите беа прикажани како Mean±SD. Резултати: Средната вредност на рН на водичките за плакнење на устата беше 5,28±0,98 (опсег: 3,24 -7,74). Повеќе од половина (n=48; 59,3%) имаа рН вредност под критичната граница 5,5. Само четири (4,9%) имаа иницијална рН ≥7. Просечно 5,75±10,29 ml (опсег: 0,01–81,20 ml) 0,1M NaOH беа потребни за неутрализација на киселите водички за плакнење. ТК варираше од 0,01 до 162,4 mmol/l, со средна вредност 11,50±20,58mmol/l. Заклучок: Значителен дел од водичките за плакнење на устата (59,3%) имаа рН вредности под критичната граница од 5,5. Вредностите на ТК варираа, при што некои водички покажаа екстремно високи нивоа на ТК. Неопходни се понатамошни истражувања за утврдување јасни насоки за безбедна употреба на овие производи, особено за истражување на поврзаноста меѓу рН, ТК и пуферскиот капацитет на плунката.

Introduction

Mouthwashes are a widely used adjunct oral hygiene element with various beneficial effects, such as: mitigating plaque-associated oral diseases, teeth whitening, management of halitosis, as well as post-surgery and post-dental treatment[1,2]. To be considered suitable adjuncts to mechanical oral hygiene, mouthwashes should be safe for prolonged use, and their potential side effects should be well understood[3]. For example, prolonged use of mouthwashes containing chlorhexidine gluconate can result in tooth staining, loss of taste sensations, tongue irritation and sore mouth[4].

Tooth erosion, a pathological dissolving of the hard dental tissues induced by chemical acid exposure unrelated to bacterial biofilm, is a known side effect of mouthwash use 3,5. The critical pH of dental enamel demineralization is approximately 5.5 and any solution with a lower pH value may cause erosion if used frequently and for prolonged periods of time[6]. In the past, media attention was directed towards mouthwashes with pH values below 5.5 and their impact on tooth erosion[3]. The pH values of many mouthwashes have been tested and the majority of them were acidic, with some of them having a pH as low as[3,4 7].

Besides pH value, titratable acidity (TA) plays a critical role when it comes to dental erosion[8,9]. While pH is easy to measure, it lacks information regarding the concentrations of undissociated acids within the analyzed solution and it only provides information considering initial hydrogen ion dissociation[10]. Many researchers indicate that TA of a solution is a more accurate measure of the erosive potential on dental hard tissues[10]. Titratable acidity measures acidity by titrating a sample with a standardized base to a pH end point[11], and it determines the ability of a buffering agent, usually OH ions, to neutralize all available acid [10]. Authors emphasize that TA is a key factor for the time that salivary pH is maintained at low levels[12]. If a certain solution has a higher TA value, then the saliva will need more time to neutralize all acids within that solution[13].

The aim of this study was to measure and analyze the pH and titratable acidity (TA) of a wide range of commercial mouthwashes available in the Republic of North Macedonia, and to assess their potential erosive effects.

Material and methods

A comprehensive market analysis was performed in the Republic of North Macedonia, between January to October 2024, including traditional markets (pharmacies, cosmetic chains, and consumer goods markets) as well as the online market. One to three packs of each mouthwash were purchased directly from vendors according to the inclusion and exclusion criteria, without requesting free samples from manufacturers or importers.

Inclusion criteria: products intended for maintaining oral hygiene, preventing oral diseases, or having a therapeutic effect; available over the counter; and in the pharmaceutical forms of either solutions intended for direct use or concentrates to be dissolved in water, regardless of their regulatory status (medicine, medical device, cosmetic product).

Exclusion criteria: tablets that dissolve in water or other liquids, chewing tablets, saliva substitutes; products containing antibiotics, steroids, parasympathomimetic saliva stimulants, topical local anesthetics, and other prescription drugs; liquids taken orally but not intended for maintaining oral hygiene; liquids in the form of sprays, toothpastes, gels, powders, foams, homeopathic products, and products without a fully available composition.

A total of 81 mouthwashes were included in the study, which are listed in Appendix A.

Concentrate mouthwashes were dissolved according to the manufacturer instructions. The measurements of pH and titratable acidity (TA) were done twice, consecutively for each mouthwash. The results presented in this study are the average value of the two measurements, presented as Mean±SD. All measurements were done by the same researchers in the Biochemical and microbiological laboratory at the Department of Oral and Periodontal Diseases, Faculty of Dentistry – Skopje, Ss. Cyril and Methodius University in Skopje.

pH

Prior to each workday in the laboratory, the pH meter LLG-pH Meter 7 (LLG-Labware, Meckenheim, Germany) was calibrated using standard solutions (pH 4 and pH 7). The washed and dried electrode of the pH meter was immersed in a beaker filled with 50 ml of the mouthwash. The pH meter gives a visual signalization on the digital screen when the measurement is stable. Before each measurement, the electrode was washed with distilled water and dried.

Titratable acidity (TA)

To calculate the TA, first, we measured the amount of 0.1M sodium hydroxide (NaOH) (strong base) required to neutralize the pH of the mouthwash, i.e. to reach a pH 7 from its original starting pH, expressed in V/ml[8]. The titration was performed by using a micropipette (TopPette Pipettor – Dragonlab, Beijing, China), 0.1M NaOH (Alkaloid AD Skopje, Skopje, Republic of North Macedonia), a magnetic stirrer (Guardian 2000, OHAUS, Parsippany, New Jersey) and the aforementioned pH meter. The average value obtained from the duplicate measurements was used to calculate the titratable acidity using the following formula according to van Swaaij BWM *et al*.[8]: mmol/l = *MR x (V1/VM) x 1000*, where MR = molar concentration of the reagent (sodium hydroxide), mol/l (base); V1 = volume of sodium hydroxide added to pH 7, in ml; VM = volume sample MW (each 50 ml). The results were expressed in mmol/l.

Data were analyzed using the statistical software IBM SPSS Statistics [24].

Results

This study included 81 mouthwashes for which pH and TA were measured. A comprehensive list of these mouthwashes with their pH and TA values expressed as Mean±SD is provided in Appendix A.

The mean pH value of the mouthwashes was 5.28±0.98, ranging from 3.24 to 7.74 (Table 1, Figure 1). More than half of the mouthwashes (n=48, 59.3%) had a pH value lower than the critical pH 5.5, which were categorized as potentially erosive.

Table 1: pH of the mouthwashes

	Mean	Std. Dev.	Min	Max	Percentiles		
					25th	50th	75th
pH	5.28	0.98	3.24	7.74	4.43	5.27	5.87

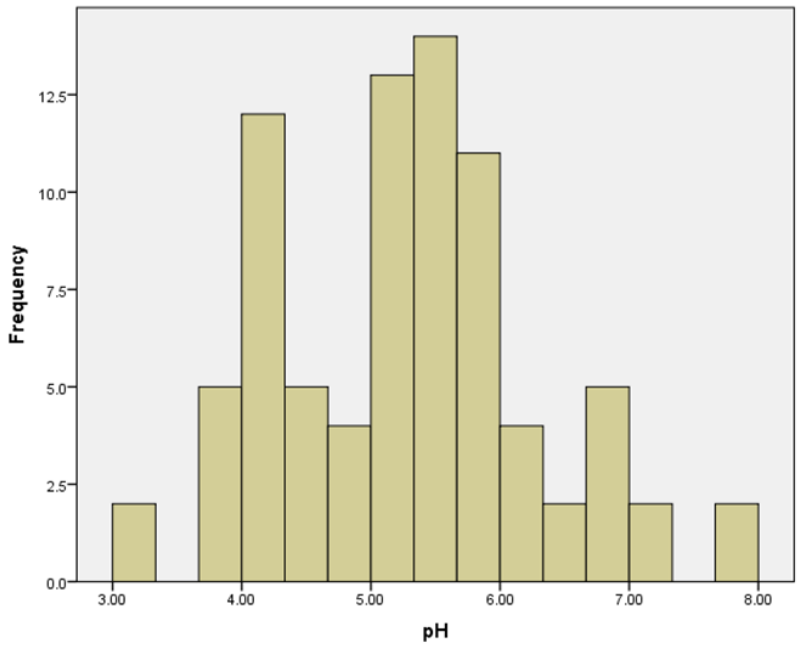


Figure 1: Distribution of pH values across the analyzed mouthwashes

Four mouthwashes (4.9%) presented an initial pH value ≥7 for which TA was not measured. A volume of 5.75±10.29 ml of 0.1M NaOH was needed to neutralize the acidic mouthwashes, ranging from 0.01 ml up to 81.20 ml (Table 2). The interquartile range (IQR) for the volume of NaOH needed to neutralize the mouthwashes was 7.2925 (0.5400–7.8325).

Table 2: Volume of NaOH used to neutralize the mouthwashes (ml)

	Mean	Std. Dev.	Min	Max	Percentiles		
					25th	50th	75th
NaOH	5.75	10.29	0.01	81.2	0.54	2.82	7.83

The titratable acidity ranged from 0.01 to 162.4 mmol/l, with a mean TA of 11.50±20.58 mmol/l (Table 3, Figure 2). The interquartile range (IQR) for titratable acidity was 14.4 (1.0800–15.4800). Outliers were identified using the 1.5 × IQR rule, with values exceeding 37.08 mmol/l considered extreme.

Table 3: Titratable acidity of the mouthwashes (mmol/l)

	Mean	Std. Dev.	Min	Max	Percentiles		
					25th	50th	75th
TA	11.5	20.58	0.01	162.4	1.08	5.65	15.48

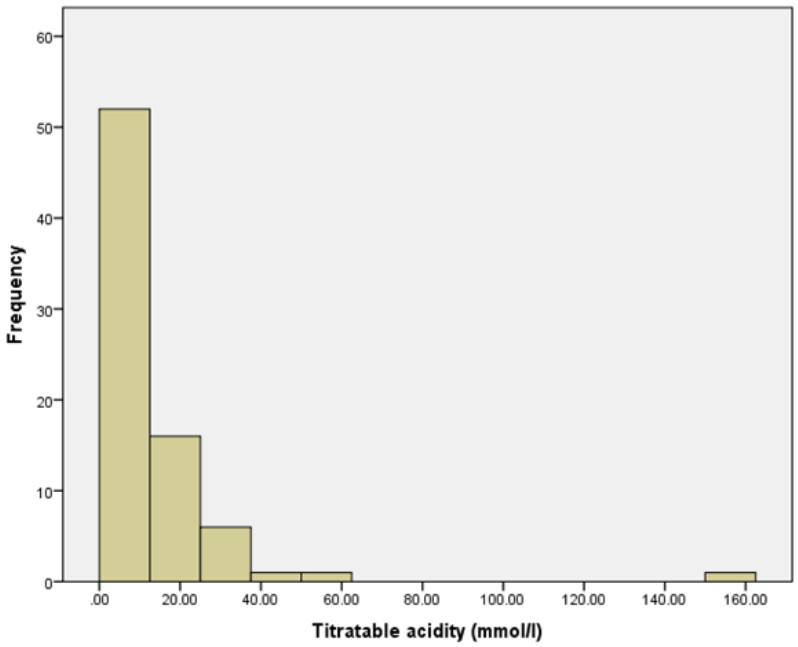


Figure 2: Distribution of titratable acidity values across the analyzed mouthwashes

Discussion

In addition to being prescribed by dentists, mouthwashes are frequently used by patients without medical supervision, who are unaware of the potential side effects of these products[14]. Usually, mouthwashes containing chlorhexidine (CHX) are associated with numerous side effects, including xerostomia, loss of taste, discoloration of the tongue, burning sensations of the tongue, and the most common concern for the patients – tooth discoloration due to the non-enzymatic Maillard reaction[15].

Dental erosion (DE) is defined as loss of the dental structure by acid dissolution that does not involve bacteria, caused by acidic substances from different sources[16]. Some mouthwashes are acidic, and data suggest that pH value and titratable acidity are two important factors which influence the erosive potential of the mouthwashes[17].

In our study, 48 of the 81 mouthwashes analyzed had a pH lower than 5.5. While it is considered that the critical pH for dental erosion is pH 5.5 for hydroxyapatite and 4.5 for fluorapatite, it is important to mention that the critical pH for dental erosion is not a fixed number and is influenced by several factors, including: frequency and duration of exposure of the acidic substance, presence of phosphates,

calcium, fluorides and other soluble solid content in the solution, titratable acidity, buffering capacity and viscosity[17–22]. It is challenging to predict the erosive potential of mouthwashes due to the fact that mouthwashes are not simple solutions and may contain molecules which inhibit the demineralization process, such as numerous natural peptides and polymers[23]. Considering low pH as a potentially erosive factor, it is important to note that even though low pH levels are harmful to the hydroxyapatite, they are important for the chemical stability of the mouthwash ingredients and facilitation of the incorporation of fluoride ions into the hydroxyapatite[8]. Some data[21] even suggest that mouthwashes with low pH increase the pH levels of plaque and saliva, suggesting that they do not have a negative impact on the saliva's buffering ability. Cavalcanti *et al.*[24] identified 3 out of 10 commercial mouthwashes as potentially erosive, B W M van Swaaij *et al.*[8] 20 out of 54, Garib *et al.*[6] out of 11 mouthwashes[17].

Since low pH plays a significant role in the incorporation of fluoride ions in the enamel, if a mouthwash has a low pH and no fluoride content it can be considered harmful to dental tissues if not used carefully[24]. Mouthwashes with low pH should not be considered for long-term use and never before brushing[25].

In addition to low pH, titratable acidity is a key factor contributing to the erosive potential of mouthwashes[17] and is considered to be a more accurate measure of the total acid content of a solution, i.e. a more realistic parameter for predicting the erosive potential of a mouthwash[26]. Mouthwashes with low titratable acidity are easily neutralized by saliva, while those with high titratable acidity cause a prolonged decrease in pH and have a larger erosive potential[25].

Among the analyzed mouthwashes in our study, three exhibited significantly high titratable acidity values, classifying them as outliers. These mouthwashes required notably higher volumes of NaOH for neutralization: 81.20 ml (Product #7), 27.67 ml (Product #29) and 22.60 ml (Product #30), corresponding to the titratable acidity values of: 162.4 (Product #7), 53.33 (Product #29) and 45.20 (Product #30).

Vivek *et al.*[26] expressed the titratable acidity as ml of NaOH needed for the pH of the mouthwashes to reach a value of 7 or higher, where the values ranged from 0.2 to 1.2 ml. A similar study by Cavalcanti *et al.*[24] used 0.1M potassium hydroxide to neutralize the mouthwashes and presented values ranging from 0.007 to 0.530. Both studies exhibited a lower range of the volume of base needed to neutralize the mouthwashes, compared to our results [5.75±10.29 ml, ranging from 0.01 ml to 81.20 ml with an IQR of 7.29 (0.54-7.83)]. Another difference between these studies is that the study by Vivek et al. included only 11 mouthwashes[26], while the study by Cavalcanti et al. included 10 mouthwashes[24], compared to the 81 mouthwashes analyzed in our study.

In contrast to the previously discussed studies that expressed titratable acidity as the volume of base required for neutralization of the mouthwashes, Swaaij *et al.*[8] expressed the titratable acidity in

mmol/l. The reported range for the titratable acidity of mouthwashes varied from 0 to 48 mmol/l. Similarly, our study also expressed titratable acidity results in mmol/. However, we observed a broader range of values, with titratable acidity varying from 0.01 to 162.40, compared to the findings of Swaaij *et al.*[8]. Goyal *et al.*[27] presented TA values ranging from 0.1 to 16.67, using 0.05N NaOH to neutralize 10 ml of the mouthwashes.

In addition to the findings presented, it is important to consider the broader regulatory and public health context surrounding mouthwash formulation and labeling. In today's global market, there is a need for precise product information[8]. The International Organization for Standardization (ISO) defined a standard regarding oral care products, specifically for oral rinses ISO 16408 (2015)[28]. ISO recommends that oral rinses should have a pH value between 3.0 and 10.5. If the pH value of an oral rinse is below 5.5 it should pass a screening test as specified in ISO 28888 (2013)[29]. This International Standard describes a screening method for assessing the erosion potential of dental hard tissues associated with the use of oral rinses and the primary aim is to provide methodology for screening oral rinses for the potential for tooth erosion. The dentist and consumer should be aware that mouthwashes may cause adverse effects[8,30].

Overall, the complexity of commercial acidic product formulations makes it difficult to separate the contributions of pH and titratable acidity from their overall effect on dental erosion[31]. We previously noted that a low pH helps maintain the stability of mouthwashes and facilitates the incorporation of fluoride ions into hydroxyapatite. However, it is essential to weigh the cost-benefit of the use of these products, as they can contribute to dental erosion. Additionally, the dynamic nature of the oral environment complicates our understanding of how mouthwashes interact with saliva. Salivary flow rate, composition, and buffer capacity could influence the dental erosion process[6,32]. Clinically, the use of such mouthwashes should be reserved for specific indications, with a great caution in patients with xerostomia, due to their diminished salivary protective capacity. These individuals should be thoroughly informed about the potential risks associated with their use[33].

Conclusion

This comprehensive study of 81 commercial mouthwashes revealed that a significant proportion (59.3%) had pH values below the critical threshold of 5.5, potentially contributing to dental erosion. The titratable acidity values varied widely, with some mouthwashes exhibiting extremely high TA levels. Further research is needed to establish clear guidelines for the safe use of mouthwashes with respect to their pH and titratable acidity values, especially to show the association between pH and TA of mouthwashes and the buffer capacity of saliva.

References

1. Radzki D, Wilhelm-Węglarz M, Pruska K, Kusiak A, Ordyniec-Kwaśnica I. A Fresh Look at Mouthwashes-What Is Inside and What Is It For? Int J Environ Res Public Health. 2022;19(7):3926. doi: 10.3390/ijerph19073926.
2. McGrath C, Clarkson J, Glenny AM, Walsh LJ, Hua F. Effectiveness of Mouthwashes in Managing Oral Diseases and Conditions: Do They Have a Role? Int Dent J. 2023;73 Suppl 2(Suppl 2):S69-S73. doi: 10.1016/j.identj.2023.08.014.
3. Pontefract H, Hughes J, Kemp K, Yates R, Newcombe RG, Addy M. The erosive effects of some mouthrinses on enamel. A study in situ. J Clin Periodontol. 2001;28(4):319-24. doi: 10.1034/j.1600-051x.2001.028004319.x.
4. McCoy LC, Wehler CJ, Rich SE, Garcia RI, Miller DR, Jones JA. Adverse events associated with chlorhexidine use: results from the Department of Veterans Affairs Dental Diabetes Study. J Am Dent Assoc. 2008;139(2):178-83. doi: 10.14219/jada.archive.2008.0134.
5. Memarpour M, Jafari S, Rafiee A, Alizadeh M, Vossoughi M. Protective effect of various toothpastes and mouthwashes against erosive and abrasive challenge on eroded dentin: an in vitro study. Sci Rep. 2024;14(1):9387. doi: 10.1038/s41598-024-59631-1.
6. Meurman JH, ten Cate JM. Pathogenesis and modifying factors of dental erosion. Eur J Oral Sci. 1996;104(2 (Pt 2)):199-206. doi: 10.1111/j.1600-0722.1996.tb00068.x.
7. Pretty IA, Edgar WM, Higham SM. The erosive potential of commercially available mouthrinses on enamel as measured by Quantitative Light-induced Fluorescence (QLF). J Dent. 2003;31(5):313-9. doi: 10.1016/s0300-5712(03)00067-8.
8. van Swaaij BWM, Slot DE, Van der Weijden GA, Timmerman MF, Ruben J. Fluoride, pH Value, and Titratable Acidity of Commercially Available Mouthwashes. Int Dent J. 2024;74(2):260-267. doi: 10.1016/j.identj.2023.09.002.
9. Benjakul P, Chuenarrom C. Association of dental enamel loss with the pH and titratable acidity of beverages. J Dent Sci. 2011;6(3):129–33. doi: 10.1016/j.jds.2011.05.001.
10. Marchan S, Hector T, Bascombe K, Marchan S, Hector T, Bascombe K. The pH and Titratable Acidity of Still and Sparkling Flavored Waters: The Effects of Temperature and Storage Time. Open J Stomatol. 2021;11(3):148–58. doi: 10.4236/ojst.2021.113012.
11. Sadler GD, Murphy PA. pH and Titratable Acidity. In: Nielsen SS, editor. Food Analysis. 4th ed. New York: Springer; 2010. p. 221–237. DOI: 10.1007/978-1-4419-1478-1_13.
12. Tenuta LM, Fernández CE, Brandão AC, Cury JA. Titratable acidity of beverages influences salivary pH recovery. Braz Oral Res. 2015;29:S1806-83242015000100234. doi: 10.1590/1807-3107BOR-2015.vol29.0032
13. Barbour ME, Lussi A. Erosion in relation to nutrition and the environment. Monogr Oral Sci. 2014;25:143-54. doi: 10.1159/ 000359941.

14. Tartaglia GM, Tadakamadla SK, Connelly ST, Sforza C, Martín C. Adverse events associated with home use of mouthrinses: a systematic review. Ther Adv Drug Saf. 2019;10:2042098619854881. doi: 10.1177/2042098619854881.

15. Brookes ZLS, Bescos R, Belfield LA, Ali K, Roberts A. Current uses of chlorhexidine for management of oral disease: a narrative review. J Dent. 2020;103:103497. doi: 10.1016/j.jdent.2020.103497.

16. Belardinelli PA, Morelatto RA, Benavidez TE, Baruzzi AM, López de Blanc SA. Effect of two mouthwashes on salivary ph. Acta Odontol Latinoam. 2014;27(2):66-71. doi: 10.1590/S1852-48342014000200004.

17. Balkees TG, Soma AT, Zainab EF. pH of Commercially Available Brands of Toothpaste and Mouthwashes in Sulaimani/ Iraq Markets: An In-vitro Study. Sulaimani Dent J. 2019;6(2):45–52. doi: 10.17656/sdj.10096.

18. Saads Carvalho T, Lussi A. Chapter 9: Acidic Beverages and Foods Associated with Dental Erosion and Erosive Tooth Wear. Monogr Oral Sci. 2020;28:91-98. doi: 10.1159/000455376.

19. Harper RA, Shelton RM, James JD, Salvati E, Besnard C, Korsunsky AM, Landini G. Acid-induced demineralisation of human enamel as a function of time and pH observed using X-ray and polarised light imaging. Acta Biomater. 2021;120:240-248. doi: 10.1016/j.actbio.2020.04.045.

20. Epple M, Enax J, Meyer F. Prevention of Caries and Dental Erosion by Fluorides-A Critical Discussion Based on Physico-Chemical Data and Principles. Dent J (Basel). 2022;10(1):6. doi: 10.3390/dj10010006.

21. Claffey N. Essential oil mouthwashes: a key component in oral health management. J Clin Periodontol. 2003;30 Suppl 5:22-4. doi: 10.1034/j.1600-051x.30.s5.8.x.

22. Lima AL, Valença AMG, Albuquerque FR, Silva NB. Analysis of pH and viscosity of commercially available fluoride mouthrinses in the city of João Pessoa/PB. Pesq Bras Odontoped Clin Integr. 2005;5:223–228.

23. Lussi A, Megert B, Shellis RP. The erosive effect of various drinks, foods, stimulants, medications and mouthwashes on human tooth enamel. Swiss Dent J. 2023;133(7-8):440-455. doi: 10.61872/sdj-2023-07-08-01.

24. Cavalcanti AL, Ramos IA, Leite RB, da Costa Oliveira M, de Melo Menezes K, Fernandes LV, de Castro RD, Vieira FF. Endogenous pH, Titratable Acidity and Total Soluble Solid Content of Mouthwashes Available in the Brazilian Market. Eur J Dent. 2010;4(2):156-9.

25. Shaik R, Reddy SP, Shaik S, Emerald S, Nemalladinne S, Sivasai D, et al. Estimation of pH, total acid and ethanol content of commercially available alcohol-containing mouthwashes and its effect on salivary pH. J. Evid. Based Med. Healthc. 2017; 4(54), 3302-3307. doi: 10.18410/jebmh/2017/656.

26. Vivek S, Shwetha R. Endogenous pH, titratable acidity of commercially available mouthwashes in Indian market. Int J Clin Trials. 2015;2(1):20–4.

27. Goyal A, Manjunath BC MB, Anup N AN, Jeph V, Bhat M, Agrawal P. Analysis Of pH, Titratable Acidity and Total Soluble Solid Content of Mouthrinses with Different Active Ingredients and Concentration Commercially Available in India: An in Vitro Study. Int J Sci Res. 2012;2(5):447–51.

28. International Organization for Standardization. Dentistry — Oral care products — Oral rinses. 2nd ed. Geneva: ISO; 2015. Report No.: ISO 16408:2015.

29. International Organization for Standardization. Dentistry — Screening method for erosion potential of oral rinses on dental hard tissues. Geneva: International Organization for Standardization; 2013. Report No.: ISO 28888:2013.

30. Raja M, Saha S, Reddy VK, Mohd S, Kumari M. Mouthwashes – an overview of current knowledge. Int J Oral Health Res Rev. 2013;1(2):24–28.

31. Fernández CE, Brandao ACS, Bícego-Pereira EC, Del Bel Cury AA, Cury JA, Tenuta LMA. Effect of pH and titratable acidity on enamel and dentine erosion. Clin Oral Investig. 2022;26(9):5867-5873. doi: 10.1007/s00784-022-04544-4.

32. Lussi A, Portmann P, Burhop B. Erosion on abraded dental hard tissues by acid lozenges: an in situ study. Clin Oral Investig. 1997;1(4):191-4. doi: 10.1007/s007840050032.

33. Hellwig E, Lussi A. Oral hygiene products, medications and drugs - hidden aetiological factors for dental erosion. Monogr Oral Sci. 2014;25:155-62. doi: 10.1159/000359942.

Appendix A: pH and TA values of the mouthwashes

	Commercial name	pH 1	pH 2	Dif	Mean	SD	B1 in ml	B2 in ml	TA 1 Mmol/L	TA 2 Mmol/L	Dif	Mean TA Mmol/L	SD
1	Doctor's Mint Mouth Wash	5.55	5.54	-0.01	**5.55**	0	**1.49**	1.49	2.98	2.98	0	2.98	0
2	Doctor's Herbal Mouth Wash	5.52	5.55	0.03	**5.54**	0.02	**1.17**	1.18	2.34	2.36	0.01	2.35	0.01
3	Doctor's Antitartar Mouth Wash	5.47	5.49	0.02	**5.48**	0.01	**0.61**	0.63	1.22	1.26	0.02	1.24	0.02
4	Doctor's Propolis Mouth Wash	5.74	5.7	-0.04	**5.72**	0.02	**0.71**	0.71	1.42	1.42	0	1.42	0
5	Doctor's Smokers Mouth Wash	5.95	5.93	-0.02	**5.94**	0.01	**0.46**	0.46	0.92	0.92	0	0.92	0
6	Alur Care Mouthwash cool mint	5.65	5.69	0.04	**5.67**	0.02	**0.7**	0.6	1.4	1.2	-0.1	1.3	0.14
7	Bilka Dent Expert Classic Parodont Protect	4	4.01	0.01	**4.01**	0	**81.4**	81	162.8	162	-0.4	162.4	0.56
8	Alverde Pro Climate 5 in 1 Mondspulung	4.65	4.67	0.02	**4.66**	0.01	**6.45**	6.89	12.9	13.78	0.44	13.34	0.62
9	Dontodent Protect & Care 10 in 1 Rundumschutz	5.66	5.7	0.04	**5.68**	0.02	**2.39**	2.48	4.78	4.96	0.09	4.87	0.12
10	Dontoent Zahnfleisch Intensiv - Pflege	5.24	5.25	0.01	**5.25**	0	**3.15**	3.08	6.3	6.16	-0.07	6.23	0.09
11	Dontodent Sensitive Intensiv - Schutz	5.04	5.06	0.02	**5.05**	0.01	**13.62**	13.31	27.24	26.62	-0.31	26.93	0.43
12	Dontodent Neue Rezeptur Mundwasser Konzentrat	3.97	3.98	0.01	**3.98**	0	**0.25**	0.26	0.5	0.52	0.01	0.51	0.01
13	Bilka Homeopathy Grapefruit Mouthwash	5.57	5.59	0.02	**5.58**	0.01	**1.95**	2.22	3.9	4.44	0.27	4.17	0.38
14	Dontodent Junior Lernneffekt - spulung	5.51	5.54	0.03	**5.53**	0.02	**1.24**	1.34	2.48	2.68	0.1	2.58	0.14
15	Dontodent Junior mund - spulung	6.01	5.96	-0.05	**5.99**	0.03	**8.12**	8	16.24	16	-0.12	16.12	0.16
16	Parodontax Active Gum Health	6.73	6.74	0.01	**6.74**	0	**0.28**	0.27	0.56	0.54	-0.01	0.55	0.01
17	Betadine Gargle	3.26	3.27	0.01	**3.27**	0	**0.55**	0.53	1.1	1.06	-0.02	1.08	0.02
18	Stomatidin	5.04	5.07	0.03	**5.06**	0.02	**1.44**	1.71	2.88	3.42	0.27	3.15	0.38
19	Oralsept	6.4	6.4	0	**6.40**	0	**0.11**	0.11	0.22	0.22	0	0.22	0
20	Elmex Caries Protection	4.43	4.44	0.01	**4.44**	0	**7.25**	7.6	14.5	15.2	0.35	14.85	0.49
21	Elmex Sensitive	4.45	4.46	0.01	**4.46**	0	**7.73**	7.7	15.46	15.4	-0.03	15.43	0.04
22	Colgate Plax Ice	5.55	5.54	-0.01	**5.55**	0	**0.26**	0.26	0.52	0.52	0	0.52	0
23	Lacalut Micellar Sensitive Mouthwash	5.45	5.5	0.05	**5.48**	0.03	**1.35**	1.46	2.7	2.92	0.11	2.81	0.15
24	Lacalut Micellar tartar protection micellar water	5.58	5.53	-0.05	**5.56**	0.03	**14.47**	14.2	28.94	28.4	-0.27	28.67	0.38
25	Listerine Total Care Clean Mint 6 in 1 Mild Taste	4.18	4.14	-0.04	**4.16**	0.02	**7.74**	8.15	15.48	16.3	0.41	15.89	0.57
26	Listerine Total Care Clean Mint 6 in 1	3.97	4.04	0.07	**4.01**	0.04	**10**	10.35	20	20.7	0.35	20.35	0.49
27	Listerine Natural Enamel protect	4.02	3.97	-0.05	**4.00**	0.03	**3.8**	3.85	7.6	7.7	0.05	7.65	0.07
28	Listerine Naturals Sabor Suave	3.85	3.85	0	**3.85**	0	**3.52**	3.83	7.04	7.66	0.31	7.35	0.43
29	Listerine Advanced Defence Sensitive	4.18	4.13	-0.05	**4.16**	0.03	**27.58**	27.75	55.16	55.5	0.17	55.33	0.24

30	Listerine Advanced White Mouthwash Mild Taste	5.98	5.97	-0.01	**5.98**	0	**22.7**	22.5	45.4	45	-0.2	45.2	0.28
31	Listerine Green Tea Mild Taste	4.03	4.04	0.01	**4.04**	0	**3.88**	3.92	7.76	7.84	0.04	7.8	0.05
32	Listerine Total Care Tartar Protect	4.23	4.3	0.07	**4.27**	0.04	**7.74**	7.74	15.48	15.48	0	15.48	0
33	Listerine Teeth&Gum Defence	4.2	4.23	0.03	**4.22**	0.02	**7.4**	7.32	14.8	14.64	-0.08	14.72	0.11
34	Listerine Smart Rinse	3.26	3.21	-0.05	**3.24**	0.03	**3.72**	3.82	7.44	7.64	0.1	7.54	0.14
35	Listerine Cool Mint	4.05	4.1	0.05	**4.08**	0.03	**4.43**	4.4	8.86	8.8	-0.03	8.83	0.04
36	Listerine Fresh Burst	3.99	3.95	-0.04	**3.97**	0.02	**1.25**	1.35	2.5	2.7	0.1	2.6	0.14
37	Astera Total All-in-one	6.25	6.25	0	**6.25**	0	**2.07**	2.17	4.14	4.34	0.1	4.24	0.14
38	Parodont Active	4.58	4.54	-0.04	**4.56**	0.02	**16.07**	15.8	32.14	31.6	-0.27	31.87	0.38
39	Oral B Pro-Expert	4.31	4.32	0.01	**4.32**	0	**0.27**	0.25	0.54	0.5	-0.02	0.52	0.02
40	Gengigel Oral Solution	6.12	6.08	-0.04	**6.10**	0.02	**3.62**	3.72	7.24	7.44	0.1	7.34	0.14
41	Colgate Cool Mint	5.41	5.37	-0.04	**5.39**	0.02	**0.39**	0.38	0.78	0.76	-0.01	0.77	0.01
42	Colgate plax white+charcoal	7.73	7.73	0	**7.73**	0					0		
43	Colgate max white	7.74	7.74	0	**7.74**	0					0		
44	Colgate plax soft mint	5.34	5.38	0.04	**5.36**	0.02	**0.4**	0.4	0.8	0.8	0	0.8	0
45	Edel+White Fresh+Protect	5.41	5.38	-0.03	**5.40**	0.02	**0.84**	0.8	1.68	1.6	-0.04	1.64	0.05
46	Lacalut Micellar Whitening Mouthwash	5.17	5.22	0.05	**5.20**	0.03	**14.15**	14.1	28.3	28.2	-0.05	28.25	0.07
47	Lacalut Multi-Effect Micellar Mouthwash	5.17	5.12	-0.05	**5.15**	0.03	**13.3**	13.45	26.6	26.9	0.15	26.75	0.21
48	Lacalut Flora	5.04	5.1	0.06	**5.07**	0.04	**2.02**	2.02	4.04	4.04	0	4.04	0
49	Lacalut Aktiv	4.33	4.32	-0.01	**4.33**	0	**4.82**	4.7	9.64	9.4	-0.12	9.52	0.16
50	Lacalut white	6.91	6.95	0.04	**6.93**	0.02	**0.43**	0.45	0.86	0.9	0.02	0.88	0.02
51	Lacalut Sensitive	4.18	4.22	0.04	**4.20**	0.02	**6.33**	6.47	12.66	12.94	0.14	12.8	0.19
52	Curaprox Perio Plus Balance CHX 0.05	5.85	5.81	-0.04	**5.83**	0.02	**0.08**	0.12	0.16	0.24	0.04	0.2	0.05
53	Curaprox Perio Plus + Protect CHX 0.12	5.74	5.74	0	**5.74**	0	**0.12**	0.14	0.24	0.28	0.02	0.26	0.02
54	Curaprox Perio Plus Forte CHX 0.20	5.62	5.65	0.03	**5.64**	0.02	**0.07**	0.12	0.14	0.24	0.05	0.19	0.07
55	Curaprox Regenerate CHX 0.09	6.94	6.95	0.01	**6.95**	0	**0.06**	0.08	0.12	0.16	0.02	0.14	0.02
56	Alkmene Tea Tree Mouthwash	5.27	5.28	0.01	**5.28**	0	**2.33**	2.32	4.66	4.64	-0.01	4.65	0.01
57	Aquafresh Fresh & Minty	6.68	6.67	-0.01	**6.68**	0	**0.44**	0.44	0.88	0.88	0	0.88	0
58	Ben & Anna Natural Mouthwash Sensitive	5.25	5.24	-0.01	**5.25**	0	**6.04**	6.01	12.08	12.02	-0.03	12.05	0.04
59	Eco Denta Refresh & Protect Mouthwash	4.76	4.78	0.02	**4.77**	0.01	**10.15**	10.35	20.3	20.7	0.2	20.5	0.28
60	Natura Siberica Whitening & Enamel Protection	5.17	5.17	0	**5.17**	0	**10.75**	10.53	21.5	21.06	-0.22	21.28	0.31
61	Natura Siberica Plaque Control & Fresh Breath	5.16	5.09	-0.07	**5.13**	0.04	**5.25**	5.44	10.5	10.88	0.19	10.69	0.26
62	Natura Siberica Strong Teeth & Gums	5.13	5.11	-0.02	**5.12**	0.01	**7.83**	8.02	15.66	16.04	0.19	15.85	0.26
63	Cosmos Organic People Mouthwash Coconut & Mint	4.96	4.96	0	**4.96**	0	**12.85**	13.16	25.7	26.32	0.31	26.01	0.43
64	Maxlab Silver Water	4.99	5.05	0.06	**5.02**	0.04	**0.28**	0.24	0.56	0.48	-0.04	0.52	0.05
65	Aquafresh Big Teeth Mouthwash	5.9	5.87	-0.03	**5.89**	0.02	**0.62**	0.56	1.24	1.12	-0.06	1.18	0.08

66	Intermed Unisept Mouth-wash	5.98	6	0.02	**5.99**	0.01	**1.21**	1.12	2.42	2.24	-0.09	2.33	0.12
67	Intermed Chlorhexil Extra 0,20% Mouthwash	5.4	5.47	0.07	**5.44**	0.04	**0.56**	0.52	1.12	1.04	-0.04	1.08	0.05
68	Intermed Chlorhexil 0.12% Mouthwash	6.12	5.92	-0.2	**6.02**	0.01	**9.06**	8.93	18.12	17.86	-0.13	17.99	0.18
69	Intermed Kids Mouthwash	4.94	4.89	-0.05	**4.92**	0.03	**2.82**	2.83	5.64	5.66	0.01	5.65	0.01
70	ESI Aloe Fresh Collutorio	4.93	4.89	-0.04	**4.91**	0.02	**10.2**	10.41	20.4	20.82	0.21	20.61	0.29
71	Limes Rosa Fresh Concen-trate	5.91	5.83	-0.08	**5.87**	0.05	**0.006**	0.01	0.012	0.02	0.004	0.016	0.005
72	Dr. Silver Mouthwash Total Care	5.27	5.24	-0.03	**5.26**	0.02	**12.4**	12.4	24.8	24.8	0	24.8	0
73	Green Fresh Concentrate Mouthwash	6.55	6.53	-0.02	**6.54**	0.01	**0.005**	0.007	0.01	0.014	0.002	0.012	0.002
74	FrezyDerm Sensitive Teeth Mouthwash	7.14	7.14	0	**7.14**	0					0		
75	FrezyDerm Plaque&Tartar Mouthwash	5.4	5.4	0	**5.40**	0	**5.65**	5.6	11.3	11.2	-0.05	11.25	0.07
76	Oral B Gum & Enamel Care Fresh Mint	4.29	4.36	0.07	**4.33**	0.04	**1.67**	1.7	3.34	3.4	0.03	3.37	0.04
77	Dental Dream Black & White	7.24	7.24	0	**7.24**	0					0		
78	Dental Dream Parodont Protect	3.9	3.95	0.05	**3.93**	0.03	**8.85**	8.92	17.7	17.84	0.07	17.77	0.09
79	Dental Dream Adcance White	4.44	4.42	-0.02	**4.43**	0.01	**3.24**	3.2	6.48	6.4	-0.04	6.44	0.05
80	Dental Dream Sensitive Teeth	6.1	6.06	-0.04	**6.08**	0.02	**3.26**	3.26	6.52	6.52	0	6.52	0
81	Dental Dream Enamel Repair	6.72	6.64	-0.08	**6.68**	0.05	**0.46**	0.49	0.92	0.98	0.03	0.95	0.04

B1=Buffer 1; B2=Buffer 2

Titratable acidity calculated at pH 7.

CASE REPORT

DRUG-INDUCED VASCULITIS WITH MULTI-ORGAN INJURY IN A SPLENECTOMISED PATIENT AND MYCOPHENOLATE MOFETIL THERAPY – A CASE REPORT

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Key words: drug-induced vasculitis, p-ANCA vasculitis, multi-organ failure, ceftriaxone, metamizole, splenectomy, mycophenolate mofetil

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Abstract

We present a case with p-ANCA positive general vasculitis and severe multi-organ injury in a splenectomised patient, which developed during ceftriaxone and metamizole administration for treatment of upper respiratory infection. Case report: A middle-aged woman with 400C fever and sore throat got a treatment with IV metamizole and ceftriaxone in a local hospital. She had a post- traumatic splenectomy 5 years ago. After metamizole, during ceftriaxone administration she felt burning in her face, developing red rush which spread over the face and darkened, later extended to her palms and feet. After visiting several clinics, she was referred finally to the University Clinic for Toxicology in Skopje. On admission, she had hypotension, hypoxemia, livid oro-pharynx, necrotic vasculitis with predominant facial distribution and unpalpable purpura on the extremities. The examinations revealed high levels of inflammatory biomarkers, anaemia, polyserositis, acute pancreatitis, hepatomegaly, acute kidney injury, disseminated intravascular coagulation, right eye vitreous haemorrhage and rhabdomyolysis. Microbiological investigations were negative. Immuno-serology showed positive p-ANCA. The acute renal failure and polyserositis resolved under methylprednisolone, meropenem, furosemide, low molecular weight heparin, fresh frozen plasma, and other symptomatic therapy, which decreased the inflammatory biomarkers, but DIC with thrombocytopenia persisted. A skin biopsy finding was inconclusive. After 25 days, the rheumatologist recommended mycophenolate mofetil with prednisolone peroral therapy during two years that resulted in stabilizing the vasculitis. The patient maintained stable after therapy discontinuation. Conclusions: Drug-induced vasculitis has the potential to induce a severe multi-organ injury with life-threatening complications. Mycophenolate mofetil procured a safe and successful treatment of drug-induced vasculitis. Splenectomy may be a potential risk factor for immunomodulated response to drugs and drugs interactions, especially during infections.

ПРИКАЗ НА СЛУЧАЈ

МЕДИКАМЕТОЗНО-ИНДУЦИРАН ВАСКУЛИТИС СО МУЛТИОРГАНСКА ПОВРЕДА КАЈ СПЛЕНЕКТОМИРАН ПАЦИЕНТ И ТЕРАПИЈА СО МИКОФЕНОЛАТ МОФЕТИЛ - ПРИКАЗ НА СЛУЧАЈ

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Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Цел на трудот е приказ на случај со p-ANCA позитивен генерализиран васкулитис и тешка повеќесистемска слабост кај спленектомизиран пациент кој се развил при администрација на цефтриаксон и метамизол за третман на горнореспираторна инфекција. Приказ на случај: Средовечна жена со треска од 400C и болки во грлото била третирана со IV метамизол и цефтриаксон во локална болница. Таа имала пост-травматска спленектомија пред 5 години. Примила метамизол, но за време на администрацијата на цефтриаксон таа почувствувала печење во лицето, развивајќи црвен осип кој се проширил по лицето и потемнувал, подоцна се проширил на дланките и стапалата. По посетата на неколку клиники, конечно била упатена на Универзитетската клиника за токсикологија во Скопје. При приемот имала хипотензија, хипоксемија, ливиден оро-фаринкс, некротичен васкулитис со доминантна дистрибуција на лицето и непалпабилна пурпура на екстремитетите. Испитувањата откриja високи воспалителни биомаркери, анемија, полисерозитис, акутен панкреатитис, хепатомегалија, акутна бубрежна повреда, дисеминирана интраваскуларна коагулација, хеморагија на стаклестото тело на десното око и рабдомиолиза. Микробиолошките наоди беа негативни. Имуносерологијата покажа p-ANCA позитивитет. Акутната бубрежна инсуфициенција и полисерозитисот се повлекоа со метилпреднизолон, меропенем, фуросемид, хепарин со ниска молекуларна тежина, свежо замрзната плазма и друга симптоматска терапија, кои ги намалија нивоата на воспалителните биомаркери, но DIC со тромбоцитопенија опстојуваше. Наодот од биопсија на кожата беше неубедлив. По 25 дена, ревматологот препорача микофенолат мофетил со преднизолон перорална терапија во текот на две години со што се стабилизираше васкулитисот. Пациентката останаа стабилни по прекинувањето на терапијата. Заклучок: Васкулитисот предизвикан од лекови има потенцијал да предизвика тешка повреда на повеќе органи со компликации опасни по живот. Микофенолат мофетил овозможи безбеден и успешен третман на васкулитисот предизвикан со лекови. Спленектомијата може да биде потенцијален ризик-фактор за имуномодулиран одговор на лекови и нивните интеракциите, особено за време на инфекции.

Introduction

Almost all drug classes have the potential to induce vasculitis which can result in tissue and organ injury. Drug-induced vasculitis (DIV) is more often associated with certain medicines, however, new drugs or sometimes their combinations have also been presented as culprit agents for vasculitis[1]. Drug-induced vasculitis (DIV) was considered as a distinct form of vasculitis and it was categorized in the group of vasculitis with probable etiology under the Chapel Hill Consensus Conference 2012 definitions for vasculitis[2] . DIV had fivefold increased incidence in the last 30 years3, and one of the assumed reasons for increased diagnosing DIV was the improved availability of immunological tests.

Small-vessel vasculitis (SVV) is the most common type of drug-induced vascular injury. Leukocytoclastic vasculitis is dominantly caused by antibiotics (including beta-lactams) and NSAID, antithyroid drugs and cocaine/levamisole [1,4], localized to skin, although renal, joint and gastrointestinal injury may also be involved. In some cases, they have been associated with antibodies, including antinuclear (ANA), rheumatoid factor and antineutrophil cytoplasmic antibodies (ANCA). Their presentation involves skin manifestations with multi-organ injuries such as interstitial lung disease, alveolar haemorrhage, interstitial nephritis and crescentic glomerulonephritis, gastrointestinal tract, retinal haemorrhage, polyserositis and ANCA against proteinase 3 (c-ANCA) or myeloperoxidase (p-ANCA), or both. ANCAs against other proteins have also been detected, but their presence is associated with other conditions beside vasculitis. Other subtypes of SVV are small vessel IgA vasculitis usually associated with drugs targeting TNF-α, then cryoglobulinaemic vasculitis and vasculitis associated with connective tissue diseases and malignancies5. Medium vessel vasculitis is usually associated with tetracycline antibiotics, while large vessel is not very typical for DIV. Treatment includes immediate drug discontinuation in mild clinical presentation, but in cases with multiorgan failure a treatment with immunosuppression is necessary with administration of cyclosporine as a first- line therapy[6].

We present a case with a general vasculitis and severe multi-organ failure in a splenectomised patient, which developed after ceftriaxone and metamizole administration and upper respiratory tract infection. The complete remission of DIC was achieved after inclusion of mycophenolate mofetil.

Case report

A middle-aged woman presented at the local hospital after a two-day fever (39.8C), sore throat, chills, general weakness. She was given crystalloids, parenteral metamizole of 2.5 gr and IV. ceftriaxone of 2 gr. During the intravenous infusion with ceftriaxone, she felt a warmth, burning and itching in her face. The symptoms first appeared on the tip of the nose and then spread to the cheeks, forehead, chin, covering the entire face. Over the next hour, the rash on her face began to turn black. At the same time, a rash began to appear on the skin of her feet and legs, arms and trunk in the form of pink-red

coloured spots. She received an additional 4 mg dexamethasone IV, 80 mg prednisolone IV and 20 mg chloropyramine IM, and was referred to the University Clinic for Infectious Diseases; afterwards they referred her to the dermatology, haematology and rheumatology clinics. After consultations with all of these specialties, due to the severity of the patient's general condition and suspicion for drug-induced vasculitis, she was referred to the University Clinic for Toxicology.

On admission, she had necrotic facial vasculitis (Picture 1), livid mucosa of oro-pharynx, non-palpable purpura on the trunk and extremities, especially gluteal region with discrete periorbital, perioral, pretibial, palmar and feet bilateral oedema with macular rush and few hematomas on the trunk and gluteus.

Picture 1. Necrotic facial vasculitis on admission



She had a history of post-traumatic splenectomy 5 years ago. Laboratory tests (Table 1) presented hypoglycaemia, rhabdomyolysis, acute kidney injury with oliguria (400 ml/24 h), and urine analysis with haematuria and disseminated intravascular coagulation (DIC) (Platelets 51x10^9/l, Di-dimer 4427 ng/ml, prolonged PT 58sec, aPTT 120 sec and TT 120 sec (ref. values PT 9.8-14.2 sec, aPTT 27.9-37.7 sec, TT 16.1-24.1 sec). C-reactive protein (CRP) increased up to 129 ng/ml and she had normal thyroid gland status (Table 1). Gas analysis from arterial blood showed metabolic acidosis compensated with respiratory alkalosis. Treatment included crystalloids up to 2000 ml/24 hours, prednisolone of 1.5 mg/kg (80 mg) IV for 1 week then 1 mg/kg, amp. Meropenem 3 gr/24 hours, amp ranitidine IV twice a day, enoxaparin 40mg s.c. twice a day and isogroup plasma 440 ml on the first day with 10 units of cryoprecipitates. During the next few days, purpura gradually intensified, acute kidney injury well responded to administration of furosemide (60 mg/day for three days

and 10 mg /day for the next five days); sodium bicarbonate was calculated by a standard formula and rehydration was controlled. Diuresis started to increase from day 3 (2000 ml /24 hours) and soon continued to polyuria during recovery of the kidney function with max diuresis of 6000 ml/24 hours. Blood urea and creatinine levels rose to maximum levels on the 5th day of hospitalisation, normalized on the 10th day and remained in reference range until the end of hospital stay (Table 1).

Day of hosp. / Parameter	1	2	3	4	5	8	9	10	11	18	25
WBC (x10^9/l) (4-9)	7	9.3	17.8	27	35	17	10	11.5	11	7.6	7.3
Er (x10^12/l) (3.6-5.2)	3.56	2.79	2.6	3.60	3.6	4.2	4.1	4.06	3.8	3.5	2.8
Hgb (g/l) (120-160)	116	92	88	123	115	139	129	128	127	118	94
PLT (x10^9/l) (150-450)	51	59	86	52	23	55	56	77	94	62	47
BUN (mmol/l) (2.7-7.8)	11.6	14.9	28	36.5	47	46	35	28	27	7.3	5.5
Creatinine (µmol/l)(45-109)	265.6	308.1	463	484	528	215	155	112	92	52	49
CK (U/l) (<173)	333	318	428						47	22	
CK-MB (U/l) (<25)	118	87		1672					13		
LDH (U/l) (<248)	1867	1726	1865	1672	894	473	470	499	450	297	232
Amylase (U/l) (30-110)	187	136	163	254		1048	855	859	733	159	142
Lipase (U/l) (30-60)						881				106	111
Troponin-I (ng/l) (<25)				325	107				22.9		12
CRP (mg/l) (<6)		129		247	130	27	19	15	14	4.6	2

Day of hosp., day of hospitalization; WBC, white blood count; Er, erythrocyte; PLT, platelet; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine phosphokinase; CK-MB creatinine phosphokinase-myocardial band; CRP, C-reactive protein.

Chest radiography presented dominantly right-sided pleural effusion, confirmed by an ultrasound, but pleural biopsy was not performed due to thrombocytopenia, which persisted during hospitalization.

The patient complained of abdominal pain from day 3 accompanied with rose of amylase(s) levels reaching the highest values on day 8 associated with an increase in lipases levels up to 881 U/l. Abdominal ultrasound (3rd day) detected ascites, congestive liver, dilated hepatic veins and inferior vena cava with a diameter of 28-30 mm with maintained blood flow, cholecystolithiasis. Ultrasound examination could not visualize the pancreas because of the increased intestinal gas collections. The kidneys were enlarged with reduced parenchymal echogenicity, with no signs of hydronephrosis. Splenectomy with accessory spleen and diameter of 20-21 mm were detected. Aminotransferase concentrations decreased after the 4th day along with normalization of

diuresis, while lipases levels reduced slowly remaining at double values of the reference range until the end of hospitalisation (Table 1). The abdomen CT on the third day of hospitalisation confirmed the ultrasound findings. Troponin increased on day 3 to 327 ng/ml and decreased on day 11 down to 22.9 ng/ml and 12.5 ng/ml on day 25. Echocardiography revealed acute pericarditis without signs of cardiac tamponade with normal ejection fraction (71%) and first degree of mitral regurgitation.

On the second day of hospitalisation, the temperature started to decrease to subfebrile (37.6 ^{o}C) and the patient was afebrile from the third day. The treatment with amp Meropenem of 3gr / 24 hours was continued for 14 days, with maximal CRP levels on the fourth day (247 mg/l) and normalization on the 15th day of stay. Microbiology analysis (haemoculture - three times, urine culture – 2 times, nasal and pharyngeal swap, Hantaan virus test, HIV, anti HCV, HBs Ag, virus panel) were negative. Immuno-serology was positive only for p-ANCA. The lactate dehydrogenase concentration, as a nonspecific marker of inflammation, was increased until the 25th day of hospitalization with maximum values of 1865 U/l, presenting prolonged tissue damage (Table 1).

During the hospital stay, platelets did not rise more than 100x 10^9/l, the lowest values being 19 x10^9/l, interpreted as a part of DIC and microvasculitis. Peripheral blood smear showed thrombocytopenia (32x10^9/l), neutrophilia 83% with “toxic granulation”, interpreted as a result of infection, fragmented erythrocytes and rare acanthocytes.

The patient was treated with enoxaparin of 0.4 mg s.c 2x1 and FFP once a day. She received 28 units of 220 ml FFP and 35 units of cryoprecipitates during the hospital stay which normalized the coagulation test (PT, aPTT and TT), corrected fibrinogen levels while DD remained increased during the whole hospitalization period (maximal concentration 7658 ng/ml to lowest concentration 2530 ng/ml). The control blood smear on the 20th day of hospitalization presented absence of toxic neutrophil granulation with increased reticulocytes 9.6x10^9/l (reference 05.- 2.5 x10^9/l). Skin biopsy was performed on the 10th day but it was inconclusive. On the 20th day, a vitreous haemorrhage on the right eye appeared although the patient was treated with LMWH and FFP. The ophthalmologist recommended continuation of the already included therapy with consecutive resorption of the haemorrhage after 2 weeks.

During the hospital stay, immunosuppressive therapy was initiated with a higher dosage of corticosteroids (methylprednisolone 1.5 mg/kg) for one week, then 1 mg/kg, without improving the platelet count, DIC and microvasculitis. The treatment of DIC included 80 mg/kg TT enoxaparin/24 hours, 8 units/50ml thrombocyte concentrates, 33 units fresh frozen plasma (220 ml/unit), 80 units of cryoprecipitates. Due to the resistance to corticosteroid and antihistaminic therapy, after 4 weeks the rheumatologist recommended mycophenolate mofetil 2 gr/day in the next 9 months and reducing to 1.5 gr/day in the following 1.5 year. Corticosteroid peroral therapy with prednisolone was gradually reduced, starting from 40 mg to 5mg /24 hours

for 10 weeks with maintaining dosage of 5 mg /24 hours. Therapy also included vitamin D, paracetamol and NSAID, and proton pump inhibitor. The patient had discrete residual facial hyperpigmentation. After 2 years, immunosuppression was discontinued and the patient has been maintained in a stable condition for the last 3 years.

Discussion

Herein we have reported a case with a severe clinical presentation of p-ANCA positive vasculitis and multiorgan injury after simultaneous exposure to drugs (ceftriaxone with metamizole) administered for treatment of upper respiratory infection in a splenectomised patient. The aetiology of primary SVV although well researched is not completely understood. However, secondary SVV may be a result of infection, malignancy and drugs including different classes of antibiotics[7]. Detecting the vasculitis aetiology in DIV is the primary goal and provides better prognosis. In cases of mixed infection with drug administration, diagnosis is often challenging. However, the cutaneous form of vasculitis in our patient developed during ceftriaxone administration very soon after she got metamizole intravenously. At the same time, cutaneous presentation progressed to severe extracutaneous manifestations and they persisted even after drug cessation, which implied that the combination of infection with medicines was the potential trigger factor. Ceftriaxone was reported as a culprit agent of DIV[8] presenting as cutaneous form or in some cases with additionally extracutaneous manifestations. Almasoudi *et al.* reviewed a large series of ceftriaxone-induced vasculitis and reported the shortest time for manifesting vasculitis (one day) unlike our case in which vasculitis appeared during ceftriaxone administration[8]. Additionally, the combination of ceftriaxone with metamizole had a nephrotoxic potential for development of AKI. Biopsy with histological confirmation of vasculitis (vascular wall infiltration with neutrophiles with fibrinoid deposition and necrosis) is considered as a gold standard for diagnosis. Nevertheless, there is a short time window of 48 hours when it can be confirmed, because after 2 days the specific findings for vasculitis started to transform. We missed this time window in our case due to prominent thrombocytopenia and could not confirm these changes with the histological examination[9]. Other authors suggest that negative pathohistological findings should not be a criterion of prime importance to exclude SVV in cases with clinical typical presentation and late performed biopsy[10].

The proposed mechanisms for betalactams and metamizole to induce allergic immune hypersensitivity reactions was through extensive reactions of T-lymphocytes or/and IgE by using hapten formation and p-i – pharmacological interaction with immune cell receptors (HLA - human leukocyte antigen) or T lymphocyte receptors[11]. But the cessation of metamizole and ceftriaxone and high corticosteroid doses in our patient did not correct the laboratory signs and clinical presentation of microvasculitis with DIC. Other group of medicines including vancomycin, NSAID, opioids, cyclosporine, ciprofloxacin, radioiodine contrast, induce DIV by

pseudo-allergic or "non-immune" reaction through activating inflammatory cells without activation of IgE or T lymphocytes[12]. The drug-induced hypersensitivity reactions have severe presentation with exanthem, fever, hematologic and visceral organ reaction. The non-immunological pathways operating by by-passing T cells activation was associated with resistance to standard immunosuppressive therapy (corticosteroids, cyclosporine, antihistamines and NSAID) and this mechanism was proposed as underlying culprit for resistant SVV[13]. The therapy with corticosteroids and anticoagulants mostly succeeded in withdrawing the clinical signs of polyserositis, acute kidney injury, rhabdomyolysis and pancreatitis in our patient, but the vasculitis and DIC did not completely resolve. Kolhie *et al.* detected resistance to corticosteroid therapy in 20% of cases with urticarial vasculitis 7. Nevertheless, adding therapy with mycophenolate mofetil improved the vasculitis parameters and clinical presentation in our patient. Mycophenolate mofetil induces inhibition of B and T cell proliferation and suppresses cell-mediated immune response, which results in stabilizing the inflammatory processes in the small vessels. Our patient received mycophenolate mofetil during the next 25 months simultaneously with gradually lowering the corticosteroid therapy. Low doses of corticosteroid with immunosuppressing agent in newly diagnosed ANCA vasculitis was as efficient as solitary high corticosteroid dose regimen in succeeding remission[14] but longer corticosteroid treatment was associated with reduced relapses as it was in this presented case [15].

Our patient had systemic symptoms and positive immunology tests for p-ANCA, but negative for all other tests in the immunology panel during hospitalization and after 2 years of follow up, considering her condition as a drug-induced vasculitis with multisystem injury. She had a history of post-traumatic splenectomy which was less often associated with infectious and thrombotic complications compared to splenectomy because of other underlying medical conditions. However, in both situations splenectomy was associated with reactions of hypersensitivity. Patients with post-traumatic splenectomy and preserved Th2 leukocyte function have been reported as prone to allergy and reaction of hypersensitivity[16] because splenectomy induces losing lien immunocytes that participate in prevention of auto- immune inflammation[17].

Conclusion

DIV is presented with cutaneous form of vasculitis but it also leads to extracutaneous manifestations with severe multi-organ failure as life-threatening complications. The awareness of DIV and early withdrawal of the culprit drug can help in early recovery and better prognosis. In severe cases, immunosuppression with mycophenolate mofetil has been safe and successful therapy for vasculitis control. Different aetiology factors of SVV affects the skin, which emphasises the importance of identifying SVV with underlying systemic autoimmune disease that need life-time medical attention. Splenectomy might be taken in consideration as a potential risk factor for immunomodulated response to

drugs and drug interactions, especially during infections.

References

1. Deshayes S, Dolladille C, Dumont A, Martin Silva N, Chretien B, De Boysson H, *et al*. A worldwide pharmacoepidemiologic update on drug-induced antineutrophil cytoplasmic antibody–associated vasculitis in the era of targeted therapies. Arthritis & Rheumatology. 2022 ;74(1):134–9. doi: 10.1002/art.41902
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, *et al*.2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11. doi: 10.1002/art.37715.
3. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol. 2022;18(1):22–34. doi: 10.1038/s41584-021-00718-8.
4. Austin K, Janagan S, Wells M, Crawshaw H, McAdoo S, Robson JC. ANCA Associated Vasculitis Subtypes: Recent Insights and Future Perspectives. J Inflamm Res. 2022; 15:2567–82. doi: 10.2147/JIR.S284768.
5. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. Intern Emerg Med. 2021;16(4):831–41. doi: 10.1007/s11739-021-02688-x.
6. Weng CH, Liu ZC. Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Chin Med J (Engl). 2019;132(23):2848–55. doi: 10.1097/CM9.0000000000000539
7. Kolkhir P, Grakhova M, Bonnekoh H, Krause K, Maurer M. Treatment of urticarial vasculitis: A systematic review. Journal of Allergy and Clinical Immunology. 2019;143(2):458–66. doi: 10.1016/j.jaci.2018.09.007.
8. Almasoudi AA, Bablghaith ES, Alaauldeen SI, M Falemban A, Sherbeeni AA, Bulkhi AA. Ceftriaxone-induced leukocytoclastic vasculitis: a case report and literature review of antibiotic-induced leukocytoclastic vasculitis. Journal of International Medical Research. 2022;50(5):030006052210977. doi: 10.1177/03000605221097768
9. Shavit E, Alavi A, Sibbald RG. Vasculitis—What do we have to know? A review of literature. Int J Low Extrem Wounds. 2018;17(4):218–26. doi: 10.1177/1534734618804982.
10. Jovanovic M, Sabovic M. Refractory drug-induced systemic small-vessel vasculitis with two varied extracutaneous manifestations: a case report and review of the literature. J Med Case Rep. 2023;17(1):470. doi.org/10.1186/s13256-023-04174-8
11. Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. Allergy. 2019;74(8):1457–71. doi: 10.1111/all.13765.
12. Mayorga C, Fernandez TD, Montañez MI, Moreno E, Torres MJ. Recent developments and highlights in drug hypersensitivity. Allergy. 2019;74(12):2368–81. doi:

10.1111/all.14061.

13. Loricera J, Blanco R, Ortiz-Sanjuan F, Hernandez JL, Pina T, Gonzalez-Vela MC, *et al.* Single-organ cutaneous small-vessel vasculitis according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides: a study of 60 patients from a series of 766 cutaneous vasculitis cases. Rheumatology. 2015;54(1):77–82. doi: 10.1093/rheumatology/keu295.
14. Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, et al. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis. JAMA. 2021;325(21):2178. doi:10.1001/jama.2021.6615
15. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody–associated vasculitis: A meta- analysis. Arthritis Care Res (Hoboken). 2010; 62(8):1166–73. doi: 10.1002/acr.20176.
16. Miniello S, Jirillo E, Cristallo G. Correlations between splenectomy and allergic symptoms. Preliminary results of a study concerning IL-4 and IgE serum level. Ann Ital Chir 2007; 78(6):499–502. PMID: 18510029.
17. Aliyu M, Zohora F, Akbar Saboor-Yaraghi A. Spleen in innate and adaptive immunity regulation. AIMS Allergy Immunol. 2021;5(1):1–17. doi: 10.3934/Allergy.2021001

CASE REPORT

AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY (APROP), TIMELY SCREENING AND APPROPRIATE TREATMENT - CASE REPORT

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Key words: retinopathy of prematurity (ROP), anti-VEGF, screening, visual acuity, APROP

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Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that is one of the leading causes of blindness in children. In this paper, we describe a case of a premature male child diagnosed with a aggressive posterior form of ROP (APROP) and treated with anti-VEGF injections in both eyes. Ophthalmological monitoring was done during several years of the child's growth. The aim is to highlight the importance of timely screening protocols in order to prevent permanent consequences on visual acuity.

ПРИКАЗ НА СЛУЧАЈ

ЗАДНА АГРЕСИВНА ПРЕМАТУРНА РЕТИНОПАТИЈА (APROP), НАВРЕМЕН СКРИНИНГ И СООДВЕТЕН ТРЕТМАН - ПРИКАЗ НА СЛУЧАЈ

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Клучни зборови: прематурната ретинопатија (РОП), анти-VEGF, скрининг, видна острина, APROP

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Печатарски права: ©2025. Игор Исјановски, Андреа Стојановска, Емилија Ѓошевска Даштевска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа ториганалниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Прематурната ретинопатија (РОП) е вазопролиферативно заболување на ретината коепретставува една од водечките причини за слепило кај децата. Во овој труд опишуваме случај на предвреме родено машко дете кое е дијагностицирано со задна агресивна форма на РОП (APROP) и истото е третирано со примена на анти-VEGF инекции во двете очи. Направен е офталмолошки мониторинг во текот на повеќе години од растот на детето. Целта е да се истакне важноста на навремените скрининг протоколи со цел спречување на трајните последици по видната острина.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that can lead to significant vision loss and even blindness. ROP is one of the leading causes of blindness in children. Globally, ROP is becoming a significant health issue, particularly in regions where premature birth rates are rising, and neonatal care is improving. The exact incidence varies, but worldwide, it's estimated that 15-20% of premature infants may develop ROP to some degree[1]. ROP is a significant concern in North Macedonia. A retrospective study analyzing data from 2010 to 2020 reported that out of 15,825 examinations conducted, screening was performed on 4,518 (11.66%) premature babies. Among these, 580 (12.84%) were diagnosed with active ROP requiring treatment. Treatment modalities included laser photocoagulation for 345 (59.48%) infants and Anti-VEGF therapy for 243 (41.9%) infants[2]. There are several stages of the disease's evolution. APROP (aggressive posterior retinopathy of prematurity) is considered the most severe form. In order to prevent complications such as retinal detachment, cataracts, glaucoma, myopia, strabismus, and amblyopia, protocols have been established worldwide for the screening and treatment of these children. There are several types of treatment, the most commonly used of which are laser photocoagulation and the application of anti-VEGF injections. Regardless of the choice of treatment, regular fundus examinations are essential to ensure that the condition of the fundus does not worsen.

Case Report

In our case report, we are talking about a premature male baby. He was born at 30 weeks of gestation with a birth weight of 2290 grams. He underwent a consultative examination at the University Clinic for Gynecology and Obstetrics in Skopje, the neonatal intensive care unit. The examination was performed by a pediatric ophthalmologist from the University Clinic for Eye Diseases in Skopje, trained in the examination and treatment of premature infants. The examination was performed at 34 weeks of gestation using an indirect ophthalmoscope and a 28-dioptre magnifying glass, a blepharostat and an indentor. The patient was administered a local anesthetic, tetracaine. During the examination, a very severe form of retinopathy of prematurity, APROP, was diagnosed. An indication for the use of anti-VEGF treatment, i.e. the application of Avastin in both eyes, was established. The application of Avastin, in both eyes, was carried out one day after the diagnosis and indication at the PHI University Clinic for Gynecology and Obstetrics. The procedure was performed under local anesthesia. The application was performed using an insulin needle in the area of 2mm from the limbus, at an angle of 90 degrees, i.e. directed towards the posterior pole of the eye. After the application, antibiotic therapy and a nonsteroidal anti-inflammatory agent were prescribed as per the protocol. A control was performed after 5 days of the application. No side effects or complications were observed. Regular controls were

performed after 2 weeks and every 2 weeks until the 41st gestational week at the PHI University Clinic for Eye Diseases. It was noted that there was no progression, but rather an improvement in the condition of the fundus. By improvement of the condition is actually meant regression of the pathological blood vessels. The prescribed therapy was then discontinued. The next control was performed when the child was 3 months old. An ultrasound examination was performed and a normal finding was noted. The ultrasound was repeated on several occasions, at an interval of 3 months. The ultrasound finding was with a normal finding of the eyeballs. Further examinations were performed in the strabismus office. The child was already 2 years old. Regular check-ups were performed every 6 months until the third year of age. At that time, a fundus examination was performed. The following findings were recorded: PNO at the level of the retina with clear boundaries and color, blood vessels with an orderly flow and lumen, macula lutea with a clear foveolar reflex. In addition to the fundus examination, refraction with cycloplegia (Atropine a 0.5%), refractometry in mydriasis were performed and the results were noted. At that examination, the child had a visual acuity of 0.8 partially in both eyes. The refraction showed a hyperopic form of astigmatism which was then corrected with distance glasses. Visual acuity of 1.0 was achieved with correction in both eyes. Since then, the child has been coming for regular 6-monthly check-ups and he has consistently had a visual acuity of 1.0 with correction in both eyes.

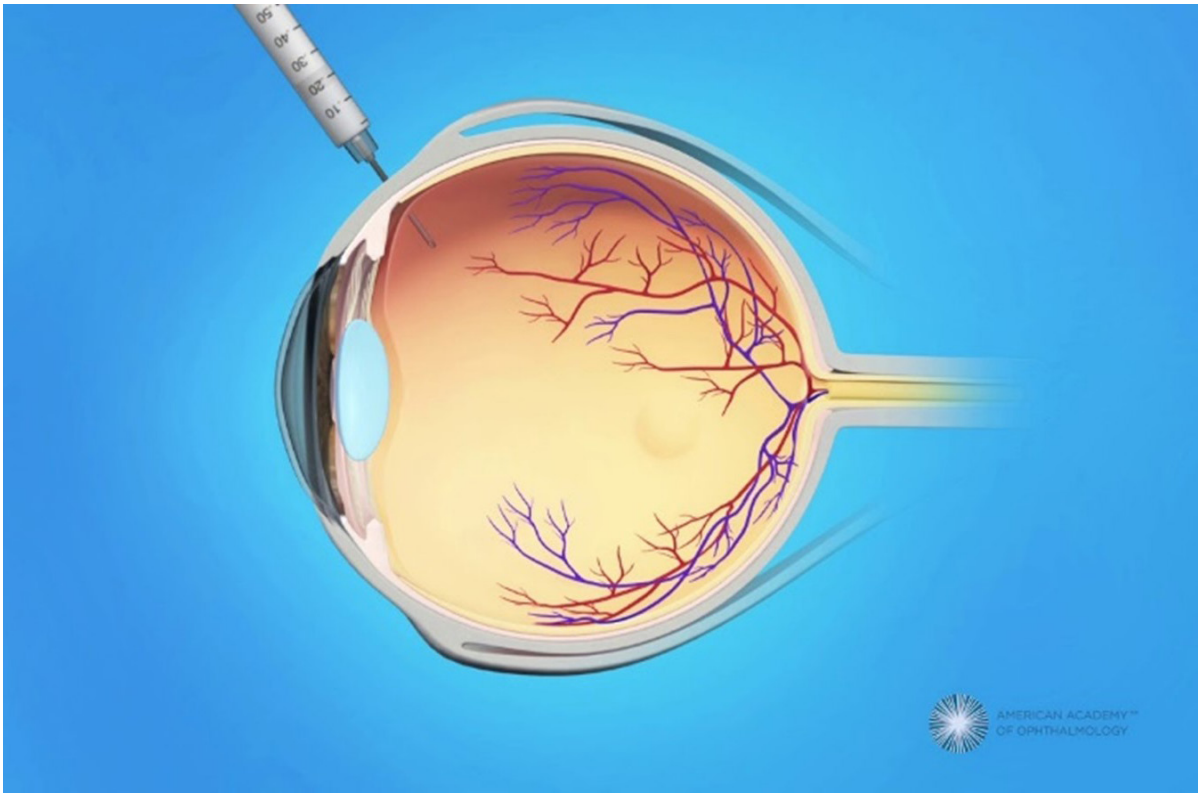


Figure 1: Application of anti-VEGF injection
Source: American Academy of Ophthalmology

Discussion

With the development of intensive care for premature babies, the survival rate of extremely premature babies is increasing. This leads to an increase in the incidence of ROP. Oxygenation, i.e. hyperoxia and hypoxia of the retina, plays a key role in the pathogenesis of the disease. It directly affects vascular endothelial growth factor (VEGF), which in turn causes abnormal growth of pathological blood vessels. The retina is the photosensitive part at the back of the eye that has blood vessels that develop gradually during fetal development. This process should be completed from 36 to 40 weeks of gestation. In premature babies, the process of retinal blood vessel development is incomplete. Blood vessels do not reach the extreme periphery of the retina, leaving an avascular zone that is extremely sensitive to oxygen concentration. Premature babies are placed in incubators with a high concentration of oxygen in neonatal intensive care units. These oxygen concentrations contribute initially to vasoconstriction of the retinal blood vessels, thereby weakening the avascular zones, which at the same time suffer from hypoxia. As a compensatory mechanism for hypoxia, vascular endothelial growth factors are secreted, which lead to the growth of new blood vessels. They are fragile and can leak and bleed, and lead to further complications such as the growth of fibrovascular membranes in the vitreous body. These membranes have the ability to contract and exert traction on the retina. This can lead to retinal detachment and loss of vision[3,4].

There are several stages of disease evolution:

Stage 1 (line of demarcation); the first sign of ROP is the formation of a thin, wavy gray-white line that is approximately parallel to the ora serrata and separates the avascular from the vascular retina. The line is noticeable at the temporal periphery and abnormal branching blood vessels can be seen leading to it.

Stage 2 (ridge); If the disease progresses, the line of demarcation develops into a raised ridge above the level of the retina.

Stage 3 (ridge with extraretinal fibrovascular proliferation); As the disease progresses from stage 2 to stage 3, the ridge acquires a pink color due to fibrovascular proliferation, which advances to the surface of the retina and invades the vitreous. It is accompanied by dilatation and tortuosity of the retinal blood vessels behind the equator. Retinal hemorrhages are common and vitreous hemorrhage may also occur.

Stage 4 (sub-total retinal detachment); occurs after progression of fibrovascular proliferation. The detachment occurs at the extreme periphery and spreads centrally. Typically develops in neonates around 10 weeks of age.

Stage 5 (total retinal detachment)

Plus disease: refers to the severity of the changes in the blood vessels in the retina. There is a worsening of the condition, with the blood vessels becoming tortuous and dilated.

Any of these changes may be located in one of three zones of the fundus: zone 1 - posterior pole, zone 2 - mid-periphery, and zone 3 - far periphery.

The most severe form is considered to be the APROP form. It is characterized by rapid and severe progression compared to other forms of ROP.

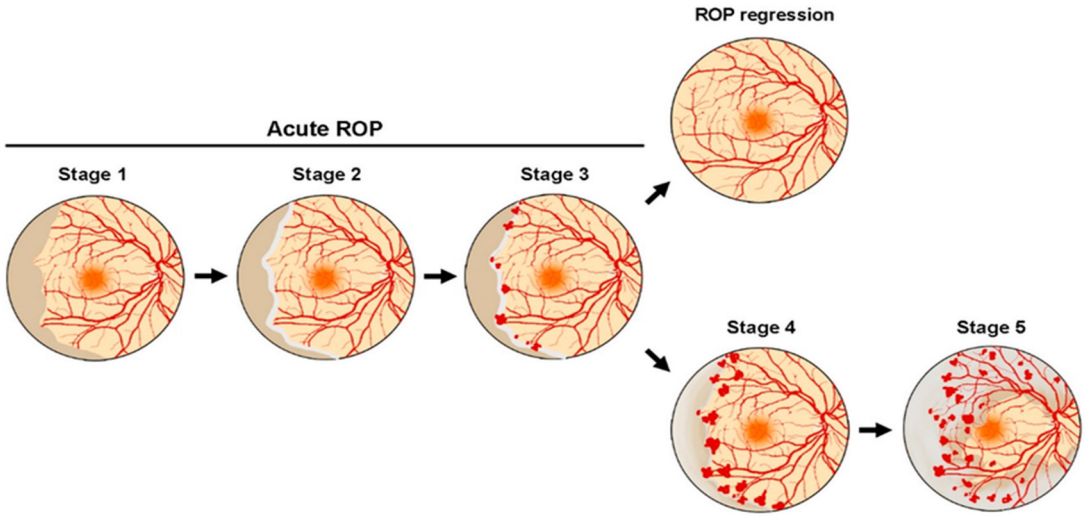


Figure 2: Stages of retinopathy of prematurity
Source: https://www.researchgate.net/figure/Schematic-representation-of-retinopathy-of-prematurity-ROP-stages-Stage-1-is_fig1_361838879

Rapid progression occurs within a few days to weeks, unlike the more common forms that progress more slowly, over a few weeks to months. Changes in the fundus are at the posterior pole and affect the center for clear vision – the macula. There is pronounced tortuosity and dilation of the blood vessels at the posterior pole, i.e. plus disease. These blood vessels are fragile, disorganized and prone to leakage and bleeding. This leads to the development of macular edema and the formation of scars on the retina. Risk factors for the occurrence of this aggressive form include low birth weight, especially below 1000 grams, gestational week, below 27 weeks, fluctuation of oxygen concentration in neonatal intensive care, infections and other medical complications, as well as race (black) and genetic factors.[5][6]

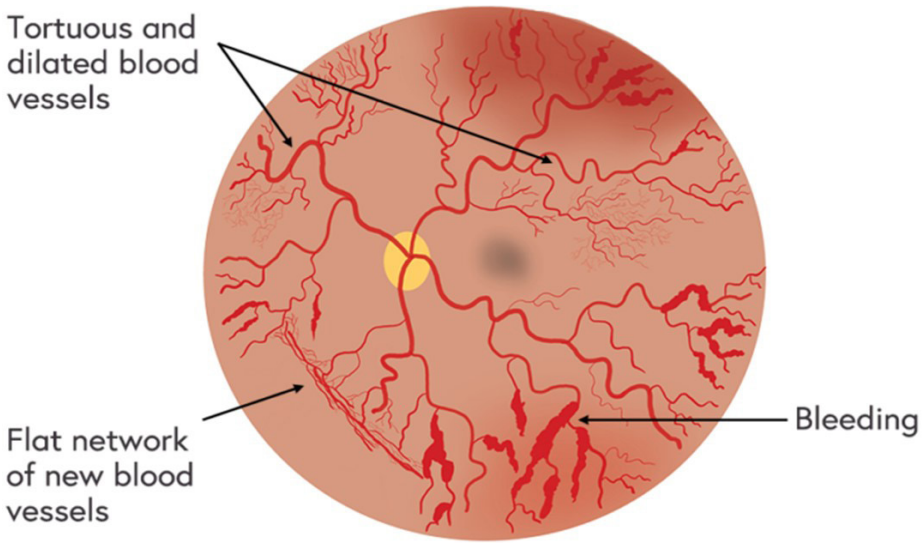


Figure 3: Aggressive posterior retinopathy of prematurity APROP
Source: https://www.futurelearn.com/info/courses/retinopathy-of-prematurity-practical-approaches-to-prevent-blindness/0/steps/90569

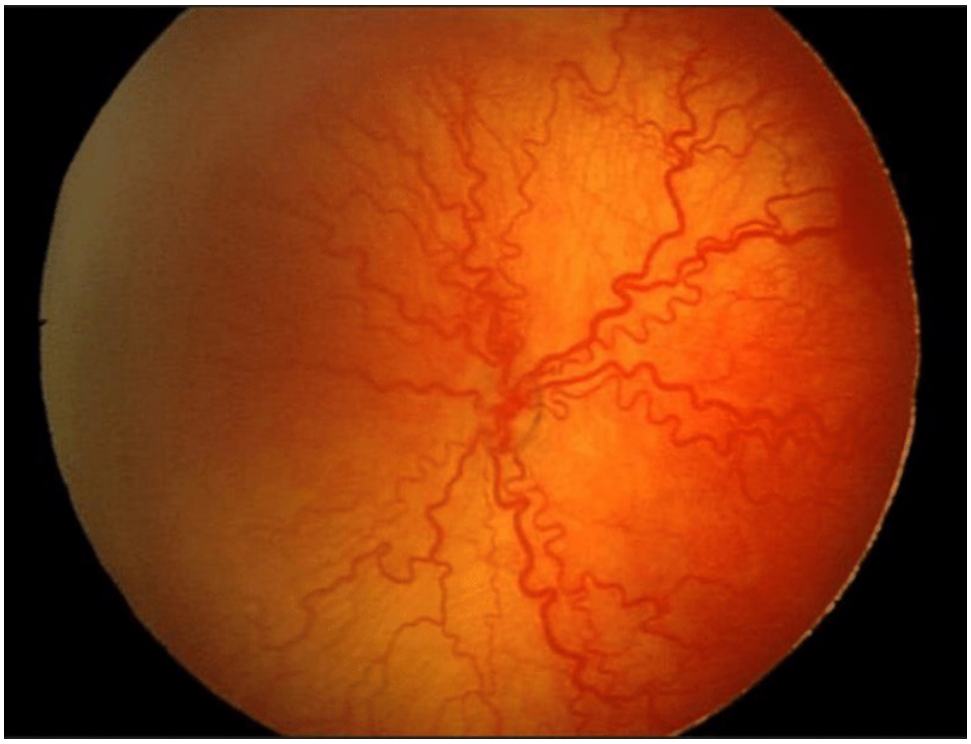


Figure 4: APROP
Source: https://www.futurelearn.com

The prognosis of APROP depends on early detection and early treatment. In terms of therapeutic modalities, the most widely used worldwide are laser photocoagulation and the application of anti-VEGF injections. Laser photocoagulation limits the already occurring changes in the periphery of the retina, while anti-VEGF treatment acts directly on VEGF receptors and inhibits the growth of new blood vessels[7]. Early treatment helps preserve central vision, although some children develop refractive errors such as myopia and astigmatism[8].

In general, complications of ROP can be divided into two groups, i.e. complications that occur soon after the diagnosis of ROP, and complications that occur several months to years later.

The American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association of Pediatric Ophthalmology and Strabismus have established direct guidelines for screening these patients. According to them, every premature baby born under 30 weeks of gestation and with a birth weight of less than 1500g should be examined with indirect ophthalmoscopy of dilated pupils[9, 10].

The purpose of screening for ROP is: early detection, identification of risk factors, monitoring of progression, determining appropriate treatment and preventing blindness. Early detection allows for the recognition of babies at risk and establishing a diagnosis when timely treatment is crucial. Timely treatment before the disease progresses to permanent stages prevents irreversible damage to the retina, thereby preserving and maintaining the normal structure and function of the retina for further complete functionality of the organ of vision[11].

Conclusion

Retinopathy of prematurity as a disease of modern and advanced medicine is one of the leading causes of blindness in children worldwide. The occurrence of ROP depends directly on the neonatal intensive care centers, the experience of the pediatric ophthalmologist, as well as the structural predispositions and factors of the eye for the development of the disease. The pathogenesis of ROP involves a delicate balance between oxygen exposure, premature retinal vascular development and excessive response to hypoxia. The most complex moment is the cellular mechanisms that lead to this condition, and we can directly influence them only through timely detection of children at risk and timely examination and treatment. Screening is a method that allows for multidisciplinary cooperation in order to provide care and a chance for excellent vision for the premature baby. However, we need experienced and professional pediatric ophthalmologists who, in suspicious cases, make the assessment and decision for treatment, and of course monitoring after treatment.

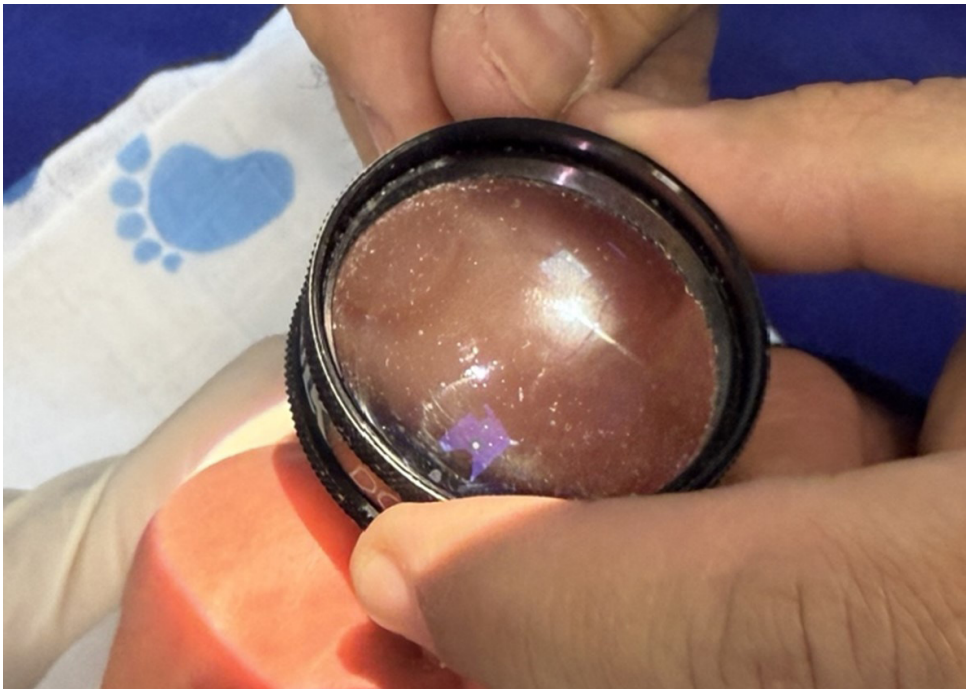


Figure 5: Fundus examination with indirect ophthalmoscope, 28-dioptre magnifying glass and indentor

References

1. 1.Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol. 1995;43:123–126
2. Tateshi B. Klenkoski S. Screening for retinopathy of prematurity in premature babies born in north macedonia – 10 years results (2010-2020). Acta Medica 2023. 82.
3. Chan-Ling T, Gole GA, Quinn GE, Adamson SJ, Darlow BA. Pathophysiology, screening and treatment of ROP: a multi-disciplinary perspective. Prog Retin Eye Res. 2018;62:77–119. doi: 10.1016/j.

preteyeres.2017.09.002

4. Smith LEH. Pathogenesis of retinopathy of prematurity. Growth Horm IGF Res. 2004;14(Suppl A):S140–S144. doi: 10.1016/j.ghir.2004.03.030
5. Narnaware SH, Bawankule PK, Raje D. Aggressive Posterior Retinopathy of Prematurity (APROP): LASER as the primary modality of treatment. J Ophthalmic Vis Res. 2021;16(3):400–407. doi: 10.18502/jovr.v16i3.9437
6. Knight-Nanan DM, Algawi K, Bowell R, et al. Advanced cicatricial retinopathy of prematurity—outcome and complications. Br J Ophthalmol. 1996;80:343–345. doi: 10.1136/bjo.80.4.343
7. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. Cochrane Database Syst Rev. 2018;1:CD009734. doi: 10.1002/14651858.CD009734.pub3
8. Holmström M, el Azazi M, Kugelberg U. Ophthalmological long-term follow up of preterm infants: a population based, prospective study of the refraction and its development. Br J Ophthalmol. 1998;82:1265–1271. doi: 10.1136/bjo.82.11.1265
9. World Health Organization. Vision 2020: Global Initiative for the Elimination of Avoidable Blindness: Action Plan 2006–2011; DOI: 10.1001/archopht.122.4.615
10. Fierson WM, Saunders RA, Good W; American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131(1):189–195
11. Knight-Nanan DM, O'Keefe M. Refractive outcome in eyes with retinopathy of prematurity treated with cryotherapy or diode laser: 3 year follow up. Br J Ophthalmol. 1996;80:998–1001. doi: 10.1136/bjo.80.11.998