

MEDICAL REVIEW

JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA

THE FIRST ISSUE WAS PUBLISHED IN 1948

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MEDICAL REVIEW is published bimonthly (six issues per year) with a circulation of 1.000 copies. The annual payment fee in 2026, for individuals from the territory of Serbia, is 4,000.00 dinars (the value-added tax included), 6,000.00 dinars for individuals from Serbia who are not members of the Society of Physicians of Vojvodina of the Medical Society of Serbia, 80 Euros for authors outside the territory of Serbia, and 9,000.00 dinars (+ VAT) for institutions. The payment account is: 340-1861-70 or 115-13858-06, "Annual subscription for Medical Review".

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The manuscripts are submitted at: aseestant.ceon.rs/index.php/medpreg/. Editorial Office Address:
Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajica 9,
Tel. 021/521-096; 063/81 33 875, E-mail: dlvslldnovisad@gmail.com; Website: www.dlv.org.rs

Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9
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Prijem rukopisa vrši se u elektronskoj formi na stranici: aseestant.ceon.rs/index.php/medpreg/. Adresa Redakcije: Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9, Tel. 021/521-096; 063/81 33 875
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LETTER FROM THE EDITOR *PISMO UREDNIKA*

Medicine between the bedside and the algorithm: reflections on the March – June issue of *Medical Review*

As I write this note for our July - August number, the preceding March–June double issue has only just reached our readers, and it rewards a second look. Read as a whole rather than as a sequence of separate papers, it offers a portrait of where clinical medicine in our region is placing its attention, and of the questions our contributors judge most worth asking. Two currents run through it with particular force, namely the arrival of computational tools at the clinical coalface and a renewed, careful attention to the individual patient, and it is around these that I should like to organise a few remarks.

The most conspicuous thread is the steady advance of artificial intelligence and digital technology into everyday practice. The issue carried an original study applying deep-learning models to the classification of colorectal adenomas, framed not merely as a technical exercise but as a proposal for redesigning pathology workflows and relieving a genuine workforce burden [1]. It was joined by a review of artificial intelligence in urodynamic studies, which weighed the promise of machine learning against the sober reality that visual interpretation by an experienced clinician remains, for now, the cornerstone of diagnosis [2]. Read together, the two pieces move from enthusiasm to appraisal, that is, from what these systems can do to how, and how cautiously, they might be brought into routine use.

Alongside this technological current runs a second, older, and no less important one: the discipline of individualised judgement. The issue opened with a thoughtful invited editorial on the estimation of renal function before zoledronate injection, arguing that when a binary safety decision turns on a narrow threshold in a frail patient, an imprecise creatinine-based estimate may simply not be good enough, which amounts to a plea, in essence, for measuring rather than assuming [3]. The same spirit animated a paediatric case report describing anaesthetic management of a child with confirmed allergy to midazolam, atropine and rocuronium, where even routine agents became a hazard and safe care depended on a bespoke

plan [4]. These are reminders that guidelines describe populations, while patients present one at a time.

Several papers speak directly to the health of our own community. Regional, single-centre experience continues to anchor the journal, whether in a four-year review of basal cell carcinoma at the University Clinical Center of Vojvodina [5], or in a seminar on the state of dental-arch supporting zones in children in Vojvodina [6]. Such work rarely makes international headlines, yet it is precisely the local reference data on which sound regional practice depends.

The remaining contributions confirm the breadth our readers have come to expect: original studies on the timing of anterior cruciate ligament reconstruction [7], on predictors of recurrent sudden cardiac arrest after defibrillator implantation [8], on the laboratory, radiological and clinical correlates of popliteal artery aneurysm thrombosis [9], on uric acid concentrations in bipolar disorder [10], on collagen and elastic fibre distribution in sarcoidosis and hypersensitivity pneumonitis [11], on hand morphometry in young adults [12] and on tibial length and torsion [13]; together with a multidisciplinary review of traumatic finger amputations [14]. The issue closed, fittingly, with a paper from the history of medicine marking 825 years since the founding of the first Serbian hospital and 850 years since the birth of its founder, Saint Sava [15], a reminder that the impulse to organise care for the sick is very old, even as its tools are very new.

Medical Review has appeared without interruption since 1948, and its usefulness has always rested on the willingness of clinicians and researchers to write down what they have learned. I thank the authors, reviewers and editorial staff whose work fills these pages, and I commend the March–June issue to our readers as a single, coherent conversation between the enduring craft of the bedside and the new instruments now placed in our hands.

Radmila Matijević
Editor-in-Chief

References

1. Cavalier E. Do we really really know renal function before zoledronate injection. *Med Pregl*. 2026;79(3-6):63-5. <https://doi.org/10.2298/MPNS2606063C>
2. Milović N, Jovančević I, Fogt TG, Valerio Isairis P, Talwar A, Fogt F. Deep learning-based classification of colorectal adeno-

mas – a data-driven model for resource efficiency. *Med Pregl*. 2026;79(3-6):67-73. <https://doi.org/10.2298/MPNS2606067M>

3. Nikolić D, Petrović K, Budinski S, Batinić N, Basta Nikolić M. Correlation of laboratory, radiological and clinical parameters in patients with popliteal artery aneurysm thrombosis – a

case-control study. *Med Pregl.* 2026;79(3-6):74-80. <https://doi.org/10.2298/MPNS2606074N>

4. Ristić V, Zrnić V, Obradović M, Milankov V, Feher A. Timing of surgery influences the result of anterior cruciate ligament re-construction. *Med Pregl.* 2026;79(3-6):81-9. <https://doi.org/10.2298/MPNS2606081R>

5. Konstantinović N, Tatalović V, Bjelan S, Tomić M, Adić M, Marinković M. Basal cell carcinoma of the skin – a four-year experience of the University Clinical Center of Vojvodina. *Med Pregl.* 2026;79(3-6):90-7. <https://doi.org/10.2298/MPNS2606090K>

6. Drakul A, Erić M, Kadar D, Radanović D, Ćorić A, Krstić J. Estimation of the tibial length and degree of tibial torsion. *Med Pregl.* 2026;79(3-6):98-103. <https://doi.org/10.2298/MPNS2606098D>

7. Savić P, Bugarinović A, Vasić V. Concentration of uric acid in patients with bipolar disorder. *Med Pregl.* 2026;79(3-6):104-8. <https://doi.org/10.2298/MPNS2606104S>

8. Savanović M, Gardić N, Gardić S, Miljković D, Lovrenski A. Comparison of collagen and elastic fiber distribution in the lungs of patients with sarcoidosis and hypersensitivity pneumonitis – a pilot study. *Med Pregl.* 2026;79(3-6):109-15. <https://doi.org/10.2298/MPNS2606109S>

9. Adić M, Adić F, Konstantinović N, Brusnjai V, Ristić A. Predictors of recurrence of sudden cardiac arrest in patients

treated with an implantable cardioverter defibrillator. *Med Pregl.* 2026;79(3-6):116-21. <https://doi.org/10.2298/MPNS2606116A>

10. Đuranović S, Krstić J, Stanić D, Drakul A, Knezi N. Morphometric analysis of the hand in young adults. *Med Pregl.* 2026;79(3-6):122-8. <https://doi.org/10.2298/MPNS2606122D>

11. Dožić F, Dimitrić Ž, Filipović Đ, Jeremić D, Radojević J, Stojanović S. Artificial intelligence in urodynamic studies. *Med Pregl.* 2026;79(3-6):129-34. <https://doi.org/10.2298/MPNS2606129D>

12. Bjelan S, Nikolić J, Ćorić A, Tatalović V, Milošević M, Bjelan S. A multidisciplinary approach to the management of traumatic finger amputations. *Med Pregl.* 2026;79(3-6):135-42. <https://doi.org/10.2298/MPNS2606135B>

13. Čomić N, Puškar N, Radumilo D, Ivić S. The state of dental arch supporting zones in children in Vojvodina. *Med Pregl.* 2026;79(3-6):143-5. <https://doi.org/10.2298/MPNS2606143C>

14. Marković N, Kelić S, Zdravković R, Milenković D, Križanović D, Preveden M. Challenges in anaesthetic care of a child with confirmed allergy to midazolam, atropine and rocuronium – a case report. *Med Pregl.* 2026;79(3-6):147-9. <https://doi.org/10.2298/MPNS2606147M>

15. Jelenković A. The first Serbian hospital – 825 years since its foundation and 850 years since the birth of its founder, Saint Sa-va. *Med Pregl.* 2026;79(3-6):151-5. <https://doi.org/10.2298/MPNS2606151J>

EDITORIAL UVODNIK

INTERVENTION THRESHOLDS IN CHRONIC NCDS WITH A FOCUS ON CARDIOVASCULAR DISEASE AND OSTEOPOROSIS

PRAGOVI INTERVENCIJE KOD HRONIČNIH NNCD SA FOKUSOM NA KARDIOVASKULARNE BOLESTI I OSTEOPOROZU

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Editorial
Uvodnik
UDK 616.71-007.234:616-036.12]-084
<https://doi.org/10.2298/MPNS2608163M>

Introduction

It is well established that the majority of the global burden of health-related morbidity and mortality arises from chronic Non-Communicable Diseases (NCDs) such as cardiovascular disease (CVD), cancer, diabetes and respiratory diseases [1]. This identification of 4 'main' NCDs by the World Health Organisation (WHO) has led to many countries prioritising these conditions, but musculoskeletal conditions, such as osteoarthritis and osteoporosis, have often received less policy attention despite their substantial burden of disability. For example, in an analysis of the global burden of disease in the United Kingdom (UK), the greatest contribution to years lived with disability was highest (30%) for those living with musculoskeletal disorders, with mental and behavioural disorders as the second most common cause [2]. However, in 2023, as part of the UN Decade of Healthy Ageing, WHO launched a new Bone Health and Ageing initiative, the primary goals of which are to develop a strategic roadmap for optimizing bone health to promote healthy ageing and to advocate for a public health strategy to prevent fractures among older people [3].

NCDs are usually multifactorial in causation, including lifestyle factors (e.g. obesity, smoking, alcohol intake, lack of exercise) and clinical or biological risk factors; the latter range across different types of factors ranging from dichotomous (Yes/No) risk factors (e.g. a family history of the disease, the presence of other associated diseases) or other contributory clinical/biological risk factors that frequently have a continuous relationship between the factor and the risk of disease outcomes (e.g. higher blood pressure and

stroke, higher cholesterol and myocardial infarction, lower bone mineral density and fracture). These continuous clinical risk factors are often classified as diseases, such as hypertension, hypercholesterolaemia and osteoporosis, using thresholds which allow examination of the prevalence of the diseases globally and regionally. Frequently, these same thresholds are used as intervention thresholds (e.g. blood pressure above 140/90mm Hg, bone mineral density (BMD) T-score ≤ -2.5) and, in many healthcare systems, the diagnosis provides access to reimbursement of treatment costs. Until now in many healthcare settings, these thresholds have often played a central role in how clinicians decide when to start, intensify or stop treatments in patients with chronic NCDs, but the main limitation is that intervention based on a single risk factor ignores the input from other risk factors. This article addresses concepts of outcome risk, approaches to defining and applying intervention thresholds, and illustrates these issues in the setting of CVD and osteoporosis.

Outcome risk in NCDs and its role in disease management

Traditionally, as noted above, pharmacological management has been based around thresholds within individual risk factors which have been characterised as independent diseases. However, the fact that this approach is focussed on intervention thresholds based on a single risk factor in a multifactorial disease is increasingly coming under scrutiny. It is increasingly recognised that the management of NCDs should be organised around quantified estimates of

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Abbreviations

NCDs	– Non-Communicable Diseases
CVD	– cardiovascular disease
WHO	– World Health Organisation
BMD	– bone mineral density
BMI	– body mass index
SBP	– systolic blood pressure
DBP	– diastolic blood pressure
MRC	– Medical Research Council
SCOOP	– Screening of Older women for Prevention
FRAX	– Fracture Risk Assessment Tool
SBP	– systolic blood pressure
ESC	– European Society of Cardiology
NICE	– National Institute for Health and Care Excellence
UK	– United Kingdom
NOGG	– National Osteoporosis Guideline Group
LAT	– lower assessment thresholds
IT	– intervention thresholds
UAT	– upper assessment thresholds

an individual's future outcome risk rather than single risk factors in isolation. In the setting of osteoporosis and the role of BMD, this distinction between its use for diagnostic and intervention thresholds was already acknowledged in the original WHO report that established the T-score threshold for osteoporosis in 1994. "As a diagnostic tool, it (BMD) gives information concerning the presence or absence of the disease with the cut-off values chosen. Its potential as a prognostic tool is to determine the future probability of osteoporosis or, better, the probability of fragility fractures where different cut-off values may be used. In this sense, bone density values are used as a risk factor. Useful analogies may be drawn with other diseases for which major risk factors have been identified" [4].

The outcome risk is usually expressed as the risk or probability that a clinically relevant event (for example myocardial infarction, stroke, osteoporotic fracture or death) will occur over a specified time horizon, most often the next 10 years. In CVD, examples of risk prediction models estimate the likelihood of events such as non-fatal myocardial infarction, stroke, or cardiovascular death using combinations of age, sex, blood pressure, lipids, smoking and diabetes, and sometimes additional biomarkers (**Figure 1**) [5–7]. In contrast to being above or below the 'diagnostic' thresholds, these models use the actual values of the continuous varia-

bles (e.g. blood pressure, cholesterol) as the input to the calculations. Similarly, in osteoporosis, fracture risk calculators such as Fracture Risk Assessment Tool (FRAX) (**Figure 1**) [8–10], QFracture [11,12] and the Garvan fracture risk calculator, [13] combine a number of clinical risk factors (e.g. age, body mass index (BMI), prior fracture, parental hip fracture, smoking, alcohol intake, glucocorticoid use, and causes of secondary causes, etc.). Unlike the FRAX and Garvan tools, QFracture does not accommodate the optional use of BMD; within the FRAX and Garvan tools, BMD is used as a continuous variable (e.g. the actual BMD or T-score) rather than simply being above or below the thresholds for BMD-defined osteoporosis.

The rationale for using outcome risk as the driver for intervention in chronic NCDs arises from several considerations. Firstly, treatment benefit is usually proportional to baseline risk: individuals at higher baseline risk gain greater absolute risk reductions for the same relative treatment effect. For example, the use of alendronate in osteoporosis is associated with a relatively consistent relative risk reduction across the spectrum of fracture risk, but with a greater absolute benefit amongst women with highest FRAX scores [14]. **In addition, some osteoporosis therapies show evidence of an increased relative efficacy in patients at higher risk [15,16]. Secondly, interventions have costs, inconvenience and potential harms, which makes it desirable to target those most likely to benefit sufficiently to justify the intervention.** Finally, the majority of health systems operate under limited resources so that prioritising high-risk groups can improve cost-effectiveness and population impact. For example, in the Medical Research Council (MRC)-funded population-based Screening of Older women for Prevention (SCOOP) study in the UK, FRAX was used to target treatment to women age 70–85 years at high risk of hip fracture. In this study, treatment was given to only 14% of women in the intervention group but led to an overall 28% reduction in hip fractures compared to standard care, an approach that was highly cost-effective/cost-saving [17–20].

Diagnostic and intervention thresholds: confusion if accepted to be identical

It is important to distinguish between diagnostic and intervention thresholds. An individual can be formally labelled as having a disease (diagnosis), but this does not automatically mean that medications or other treatments are legally or clinically required (intervention). The diagnosis usually means that management, but not necessarily treatment, is required. For diseases arising from risk factors that have a continuous relationship to a clinical outcome, diagnostic

European HeartScore	ASCVD (US) model	FRAX model
• Age • Sex • Currently Smoker? • Systolic BP (mm Hg) • Total Cholesterol (mg/dL) • HDL Cholesterol (mg/dL)	• Age • Sex • Currently Smoker? • Systolic BP (mm Hg) • On Hypertension Treatment? • Diabetes? • Total Cholesterol (mg/dL) • HDL Cholesterol (mg/dL) • Race/ethnicity	• Age • Sex • Currently Smoker? • Prior fracture? • Parental hip fracture? • Glucocorticoid use? • Rheumatoid arthritis? • Secondary osteoporosis? • Alcohol excess? • BMD (femoral neck – optional)

Figure 1. Variables included in examples of CVD risk assessment tools and the FRAX tool for osteoporosis

thresholds provide an operational definition of the disease, such as hypertension or osteoporosis, to aid classification and epidemiological surveillance of the disease, but do not necessarily specify when treatment should start. The conflation of diagnostic thresholds and intervention thresholds, frequently complicated by healthcare payers deciding to only reimburse medication costs when the diagnosis is present, can cause confusion in clinical practice in a number of ways. Firstly, the belief that diagnosis and intervention are inextricably linked implies that if the intervention threshold needs to be altered, then the disease needs to be redefined with new diagnostic thresholds. An example was provided in the 2017 ACC/AHA Guideline for High Blood Pressure in which the guidance moved away from the long-established diagnostic threshold of systolic blood pressure (SBP)/diastolic blood pressure (DBP) of $\geq 140/90$ mmHg and redefined hypertension as stage 1 hypertension (SBP 130-139/DBP 80-89 mmHg) and stage 2 hypertension (SBP/DBP $\geq 140/90$ mmHg) [21]. Despite zero change in the absolute risk of stroke, this suggested change in thresholds had a potentially dramatic impact on the global prevalence of hypertension. For example, in a study of over 4 million adults participating in the global May Measurement Month initiative, the new thresholds increased the prevalence of hypertension by 72% among the participating countries, an impact that was most pronounced in low-income countries and raised questions about the need for further epidemiological studies in dedicated population studies [22].

A similar approach to 'better' target interventions in osteoporosis has been suggested, but the latter promotes the setting of different country-specific or population-specific T-score thresholds so that osteoporosis BMD-based definitions would be numerous and confusing [23]. The desire to alter or adapt the T-score was so that the T-score threshold would be set at the value that represented the same absolute risk of fracture across populations. However, the objective of the T-score definition was to allow comparison of the prevalence of BMD below a certain threshold, rather than define a threshold of fracture risk. Of course, BMD is an important risk factor for fracture but the incidence of the latter is influenced by many other factors, some of which are known and others not yet well-defined, with variability between and across populations. The variability in fracture risk between different populations and ethnicities is much greater than the variability in BMD [24,25]. This is recognised by the need for numerous FRAX models which calibrate the risk assessment to the actual age and sex-specific incidence of fracture and mortality within different populations and ethnicities.

Limitations of single risk factor thresholds in multifactorial diseases

An important conceptual distinction is the difference between the risk arising from a single risk factor defined disease (e.g. hypertension as defined by set systolic and diastolic blood pressures or osteoporosis as defined by BMD T-scores) and the risk of the actual clinical outcomes attributable to a combination of that disease and other risk factors. Until recently, intervention thresholds have been established and used for reimbursement in these single risk factor diseases (e.g. hypertension, hyperlipidaemia, osteoporosis), a decision that impacts on the actual risk profile of the population treated in terms of their risk of the disease outcome as it disregards the presence or absence of other risk factors. Increasingly, contemporary guidelines are recommending that treatment thresholds should embrace the actual outcome risk, expressed in terms of predicted absolute CVD or fracture risk, rather than isolated blood pressure or BMD cut-offs. An example of the data analysis that supports this approach was a published meta-analysis of treatments for hypertension using individual-level data from 48 randomised trials of pharmacological blood pressure lowering medications versus placebo or other classes of blood pressure-lowering medications [26]. **Data were pooled to investigate the effects of blood pressure-lowering treatment in participants, with and without prevalent cardiovascular disease, overall and across seven systolic blood pressure categories (ranging from <120 to ≥ 170 mm Hg). In a total of 344 716 participants from 48 randomised clinical trials, 31 239 (9.8%) of participants with previous cardiovascular disease and 14 928 (8.0%) of individuals without previous cardiovascular disease had a baseline SBP of less than 130 mm Hg. In participants with and without previous cardiovascular disease, the incidence rate for developing a major cardiovascular event was lower in the intervention groups than in the comparator group with similar reductions of cardiovascular events per 5 mm Hg reduction in SBP across the two groups. Importantly, in the SBP stratified analyses, there was no reliable evidence of heterogeneity of treatment effects on major cardiovascular events by baseline cardiovascular disease status or systolic blood pressure categories (data from those without baseline cardiovascular events shown in **Figure 2**). The authors concluded that a fixed degree of pharmacological blood pressure lowering is similarly effective for primary and secondary prevention of major cardiovascular disease, even at blood pressure levels currently not considered for treatment. They concluded that the findings should dismiss "the suggestions that blood pressure-lowering treatment is only effective when**

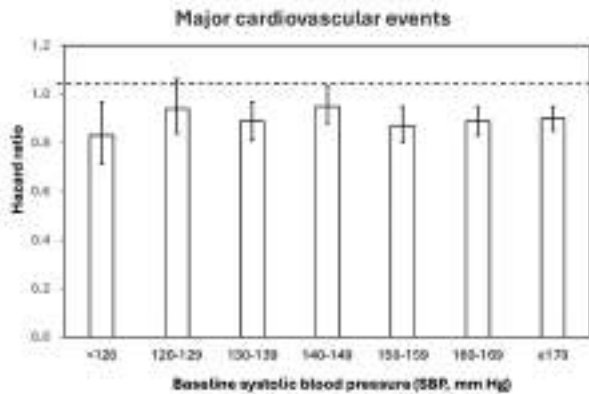


Figure 2. Effect of anti-hypertensive treatment on the risk of cardiovascular events across categories of baseline SBP in patients without previous CVD at baseline. There was no significant interaction of efficacy with baseline SBP (unadjusted interaction p-value 0.66, adjusted 1.0) with similar reductions in events at low and high baseline SBP. Adapted from [26].

blood pressure is above a certain threshold”, an erroneous belief that has been mirrored in the claims that treatments of osteoporosis are ineffective in patients with BMD values above the T-score threshold of -2.5 [27]. In osteoporosis there is now overwhelming evidence that treatments are similarly effective in many patients and clinical scenarios where the BMD is not osteoporotic [27]. This is in keeping with the recognition in the WHO 1994 report that different thresholds could be used to target interventions when BMD is used as a predictor of fracture risk rather than simply defining the presence of BMD-defined osteoporosis [4]. A further paper from key authors in the hypertension study reported above, subsequently published a paper calling for an increasing role of CVD risk prediction in clinical practice for BP treatment allocation and a cultural shift in how blood pressure is treated; “It is time for us to recognize that the objective is to treat cardiovascular disease risk not just hypertension” [28].

Intervention thresholds using outcome risks

In contrast to a diagnostic threshold, an intervention threshold can generally be characterised as the level of predicted outcome risk at which the expected benefits of a preventive or therapeutic intervention are judged to outweigh the harms and costs. As outcome risk is typically modelled as a continuous variable, clinical decision-making therefore requires choosing cut-offs or “thresholds” that translate a continuum of risk into discrete categories such as low, intermediate, high or very high risk. Different methods of deciding such thresholds are used in practice, including purely

clinical thresholds (based on expert consensus about benefit–harm trade-offs), cost-effectiveness thresholds (incorporating formal economic modelling), and pragmatic or policy thresholds that reflect local resources and priorities.

Intervention thresholds may be expressed as fixed or age-dependent risk thresholds. In the management of CVD, most international guidelines endorse fixed risk thresholds across the age range [29]. However, the 2021 European Society of Cardiology (ESC) CVD prevention guidelines introduced new age-specific risk thresholds for primary prevention, to address the concern that uniform age-independent cut-offs could result in over-treatment of older adults and under-treatment of younger adults [30]. This approach was subsequently reversed in the 2024 ESC guidelines for the management of elevated BP and hypertension which returned to a single age-independent CVD risk threshold because of concerns that the age-dependent approach could withhold CVD preventive treatment for older adults based solely on age [29,31].

A systematic review of FRAX-based thresholds identified that most guidelines used fixed or age-independent thresholds for major osteoporotic fracture and hip fracture [32]. Many guidelines use thresholds derived from a US threshold cost-effectiveness analysis which generated thresholds of 20% for MOF and 3% for hip [33], despite the fact that this cost-effectiveness analysis is now out-of-date and the thresholds may not be appropriate for lower risk countries or ethnicities. The impact of basing intervention thresholds on cost-effectiveness analysis can lead to controversial outcomes as illustrated by a NICE analysis of bisphosphonate treatments in osteoporosis in the United Kingdom (UK) in 2017. [34]. This recommended that, amongst individuals who qualify for osteoporosis assessment on the basis of the previously published National Institute for Health and Care Excellence (NICE) Fracture Risk Assessment Clinical Guideline (CG146, [35] treatment with oral bisphosphonates could be instituted at a 10-year probability of major osteoporotic fracture above 1%, or above 10% for intravenous bisphosphonates, thresholds which could have caused confusion as potential intervention thresholds [36].

As noted above in the CVD field, age-independent thresholds can impact on the equity of access to treatment across age ranges. In practice, they generally decrease access at younger ages and may lead to overtreatment at older ages [37]. To counter this, age-dependent intervention thresholds are utilised in many guidelines, initially led by the National Osteoporosis Guideline Group (NOGG) in the UK. These thresholds are clinical thresholds based on the consensus that if a woman with a prior fracture can be considered for intervention,

then a patient of the same age without a fracture but the same level of fracture risk should also be considered for treatment. This permits identification of those at highest risk at all ages so that treatment can be introduced not only to decrease that risk in the short-term but to also limit the increase in risk over time [38].

The UK National Osteoporosis Guideline Group has operationalised this approach by defining age-specific lower assessment thresholds (LAT), intervention thresholds (IT) and upper assessment thresholds (UAT) based on FRAX-estimated 10-year fracture probabilities [39–41]. In the latest NOGG guidelines, a “very high risk” category, using a FRAX-based fracture probability exceeding the intervention threshold by 60%, has also been defined to identify patients who should be referred to specialist services for more intensive assessment and treatment planning, particularly with attention to bone-forming agents as first line therapy.

Summary and Conclusion

The decoupling of diagnostic and intervention thresholds has several important clinical implications. First, it legitimises offering treatment to individuals who do not meet the bone mineral density definition of osteoporosis but have fracture probability above the intervention threshold, such as younger adults without prior fragility fracture and “osteopenic” bone mineral density but with one or more other clinical risk factors. Second, it avoids automatic treatment of all individuals with bone mineral den-

sity T-score ≤ -2.5 , particularly older patients whose absolute fracture risk may be modest compared to the wider age-matched population. Nonetheless, the co-existence of diagnostic and intervention thresholds can create confusion among clinicians and patients. Some may incorrectly equate a diagnosis of osteoporosis with an obligation to treat pharmacologically, while others may falsely reassure high-risk individuals with “normal” or “osteopenic” bone mineral density, overlooking elevated fracture risk due to age and other clinical risk factors. Under-treatment remains a significant problem, with large proportions of high-risk individuals not receiving osteoporosis medications despite clear guideline indications.

However, it is increasingly clear that outcome risk and intervention thresholds offer a coherent framework for prioritising prevention and treatment in chronic non-communicable diseases, including cardiovascular disease and osteoporosis. Despite methodological and implementation challenges, risk-based thresholds enable more rational, transparent and cost-effective use of limited healthcare resources, provided they are regularly updated (without having to redefine the disease), locally calibrated and applied with sound clinical judgement. As populations age and the burden of chronic NCDs continues to rise, coherent and well-implemented strategies for defining and applying outcome-based intervention thresholds will be essential for maximising health gains and minimising the harms and costs of both under- and over-treatment.

References

1. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: World Health Organization; 2013.
2. Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9871):997-1020.
3. World Health Organization. Fragility fractures. Geneva: World Health Organization; 2023.
4. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization; 1994.
5. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-37.
6. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S49-73.
7. Park S, Kim YG, Ann SH, Cho YR, Kim SJ, Han S, et al. Prediction of the 10-year risk of atherosclerotic cardiovascular disease in the Korean population. *Epidemiol Health*. 2023;45:e2023052.
8. Kanis JA, Johansson H, Harvey NC, McCloskey EV. A brief history of FRAX. *Arch Osteoporos*. 2018;13(1):118.
9. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. *Bone*. 2009;44(5):734-43.
10. Johansson H, Kanis JA, Oden A, Johnell O, McCloskey E. BMD, clinical risk factors and their combination for hip fracture prevention. *Osteoporos Int*. 2009;20(10):1675-82.
11. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ*. 2012;344:e3427.
12. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFracture Scores. *BMJ*. 2009;339:b4229.
13. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. *Osteoporos Int*. 2007;18(8):1109-17.
14. Donaldson MG, Palermo L, Ensrud KE, Hochberg MC, Schousboe JT, Cummings SR. Effect of alendronate for reducing fracture by FRAX score and femoral neck bone mineral density: the Fracture Intervention Trial. *J Bone Miner Res*. 2012;27(8):1804-10.

15. McCloskey EV, Johansson H, Oden A, Austin M, Siris E, Wang A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX(R). *J Bone Miner Res.* 2012;27(7):1480-6.
16. McCloskey EV, Johansson H, Harvey NC, Lorentzon M, Shi Y, Kanis JA. Romosozumab efficacy on fracture outcomes is greater in patients at high baseline fracture risk: a post hoc analysis of the first year of the frame study. *Osteoporos Int.* 2021;32(8):1601-8.
17. Shepstone L, Lenaghan E, Cooper C, Clarke S, Fong-Soe-Khioe R, Fordham R, et al. Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. *Lancet.* 2018;391(10122):741-7.
18. McCloskey E, Johansson H, Harvey NC, Shepstone L, Lenaghan E, Fordham R, et al. Management of patients with high baseline hip fracture risk by FRAX reduces hip fractures-a post hoc analysis of the SCOOP study. *J Bone Miner Res.* 2018;33(6):1020-6.
19. Turner DA, Khioe RF, Shepstone L, Lenaghan E, Cooper C, Gittoes N, et al. The cost-effectiveness of screening in the community to reduce osteoporotic fractures in older women in the UK: economic evaluation of the SCOOP study. *J Bone Miner Res.* 2018;33(5):845-51.
20. Söreskog E, Borgström F, Shepstone L, Clarke S, Cooper C, Harvey I, et al. Long-term cost-effectiveness of screening for fracture risk in a UK primary care setting: the SCOOP study. *Osteoporos Int.* 2020;31(8):1499-506.
21. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2018;138(17):e484-594.
22. Nolde JM, Beaney T, Carnagarin R, Schutte AE, Poulter NR, Schlaich MP. Global impact of different blood pressure thresholds in 4 021 690 participants of the may measurement month initiative. *Hypertension.* 2022;79(7):1497-505.
23. Wang YXJ, Griffith JF, Blake GM, Diacinti D, Xiao BH, Yu W, et al. Revision of the 1994 World Health Organization T-score definition of osteoporosis for use in older East Asian women and men to reconcile it with their lifetime risk of fragility fracture. *Skeletal Radiol.* 2024;53(4):609-25.
24. McCloskey EV, Dey A, Parr RM, Aras N, Balogh A, Bostock J, et al. Global variations in peak bone mass as studied by dual-energy X-ray absorptiometry. *J Radioanal Nucl Chem.* 2004;259(2):341-5.
25. Leslie WD. Clinical review: ethnic differences in bone mass-clinical implications. *J Clin Endocrinol Metab.* 2012;97(12):4329-40.
26. Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet.* 2021;397(10285):1625-36.
- Rad je primljen 9. IX 2026.
- Prihvaćen za štampu 9. IX 2026.
- BIBLID.0025-8105:(2026):LXXIX:7-8:163-168.
27. McCloskey E. A BMD threshold for treatment efficacy in osteoporosis? A need to consider the whole evidence base. *Osteoporos Int.* 2016;27(1):417-9.
28. McCarthy CP, Jackson R, McEvoy JW, Rahimi K. From treating hypertension to lowering cardiovascular disease risk. *Hypertension.* 2024;81(8):1655-8.
29. McCarthy CP, Rahimi K, McEvoy JW. Age-stratified risk categories for cardiovascular disease prevention therapies. *JAMA Cardiol.* 2024;9(12):1069-70.
30. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol.* 2022;29(1):5-115.
31. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J.* 2024;45(38):3912-4018.
32. Kanis JA, Harvey NC, Cooper C, Johansson H, Oden A, McCloskey EV, et al. A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. *Arch Osteoporos.* 2016;11(1):25.
33. Tosteson AN, Melton LJ 3rd, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, et al. Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int.* 2008;19(4):437-47.
34. National Institute for Health and Care Excellence. Bisphosphonates for treating osteoporosis [Internet]. 2017 [updated 2019 Jul 8; cited 2026 Sep 5]. Available from: <https://www.nice.org.uk/guidance/ta464/resources/bisphosphonates-for-treating-osteoporosis-pdf-82604905556677>
35. National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. Clinical guideline 146. London: National Clinical Guideline Centre at the Royal College of Physicians; 2012.
36. Harvey NC, McCloskey E, Kanis JA, Compston J, Cooper C. Cost-effective but clinically inappropriate: new NICE intervention thresholds in osteoporosis (Technology Appraisal 464). *Osteoporos Int.* 2018;29(7):1511-3.
37. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int.* 2013;24(1):23-57.
38. Matijević R. Osteoporosis – treatment gap. *Med Pregl.* 2022;75(Suppl 2):19-21.
39. Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas.* 2009;62(2):105-8.
40. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos.* 2017;12(1):43.
41. Gregson CL, Armstrong DJ, Bowden J, Cooper C, Edwards J, Gittoes NJL, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos.* 2022;17(1):58.

ORIGINAL STUDIES ORIGINALNI NAUČNI RADOVI

THE BURDEN OF FLUID CREEP IN THE EARLY POSTOPERATIVE PERIOD AFTER ELECTIVE SURGERY IN PATIENTS REQUIRING ADMISSION TO THE INTENSIVE CARE UNIT

ZNAČAJ TEČNOSTI KOJE SE KORISTE ZA RASTVARANJE LEKOVA U RANOM POSTOPERATIVNOM PERIODU NAKON ELEKTIVNE HIRURGIJE KOD PACIJENATA KOJI ZAHTEVAJU PRIJEM U JEDINICU INTENZIVNE NEGE

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Original study
Originalni naučni rad

UDK 616-089.168-052:615.015.14
<https://doi.org/10.2298/MPNS2608169Z>

Abstract

Introduction. Fluid creep refers to intravenous fluids used in every critically ill patient as part of routine care, including fluids administered as vehicles for medication or electrolytes, or small volumes used to keep venous lines open. It represents an additional and often unrecognised source of fluid and electrolyte load. We aimed to quantify and characterise fluid creep in our surgical Intensive Care Unit and determine its contribution to water, sodium, and chloride burden. **Material and Methods.** This prospective observational study was conducted at the University Clinical Center of Vojvodina over 60 days. A total of 53 patients undergoing elective surgery and requiring at least 48 hours of postoperative intensive care were included. Daily fluid creep volume and composition were recorded, and the electrolyte load was calculated using manufacturer-reported sodium and chloride concentrations. **Results.** The only fluid used for fluid creep was 0.9% sodium chloride. Fluid creep accounted for 19% of total daily fluid volume on postoperative day 0 and 24% on postoperative day 1. Its contribution to total sodium and chloride load increased from 17% to 30%. After 48 hours, B-lines on lung ultrasound and peripheral oedema were observed in 51% of patients. **Conclusion.** Fluids used as drug vehicles represent a substantial proportion of total intravenous fluid administration and significantly contribute to sodium and chloride load. Recognition of fluid creep may improve fluid management in postoperative intensive care patients.

Key words: Postoperative period; Intensive Care Units; Infusions; Intravenous; Fluid Therapy; Water-Electrolyte Balance; Sodium Chloride; Drug Carriers; Drug Administration Routes; Pulmonary Edema

Introduction

Postoperative fluid and electrolyte management is a key component of perioperative care. Individual-

Sažetak

Uvod. Tečnosti za rastvaranje lekova predstavljaju intravenske tečnosti koje se rutinski primenjuju kod svih kritično obolelih bolesnika i obuhvataju tečnosti koje se koriste kao rastvarači za lekove i elektrolite, kao i manje zapremine namenjene održavanju prohodnosti venskih linija. Predstavljaju dodatni i često neprepoznat izvor unosa tečnosti i elektrolita. Cilj studije bio je kvantifikovati i kvalifikovati količinu i vrstu prepisanih tečnosti za rastvaranje lekova u našoj hirurškoj jedinici intenzivne nege, kao i odrediti njihov doprinos ukupnom opterećenju vodom, natrijumom i hloridima. **Materijal i metode.** Ova prospektivna opservaciona studija sprovedena je u Univerzitetском kliničkom centru Vojvodine tokom 60 dana. Uključena su 53 bolesnika podvrgnuta elektivnim operacijama što je zahtevalo najmanje 48 sati postoperativnog lečenja u Jedinici intenzivnog lečenja. Dnevni volumen i sastav tečnosti za rastvaranje lekova su beleženi, a unos elektrolita putem ovih tečnosti izračunat je na osnovu koncentracija natrijuma i hlorida koje je naveo proizvođač. **Rezultati.** Jedina intravenska tečnost koja je korišćena u ovu svrhu bio je 0,9% natrijum-hlorid. Tečnosti za rastvaranje lekova činile su 19% ukupnog dnevnog unosa intravenskih tečnosti nultog postoperativnog dana i 24% prvog dana. Njihov udeo u ukupnom unosu natrijuma i hlorida povećao se sa 17% na 30%. Nakon 48 časova, B-linije na ultrazvuku pluća i periferni edemi registrovani su kod 51% bolesnika. **Zaključak.** Tečnosti koje se koriste kao rastvarači za lekove čine značajan deo ukupne intravenske terapije i značajno doprinose unosu natrijuma i hlorida. Prepoznavanje značaja ovih tečnosti može unaprediti njihovu preskripciju kod postoperativnih bolesnika u Jedinici intenzivnog lečenja.

KLjučne reči: postoperativni period; jedinice intenzivne nege; intravenske infuzije; terapija tečnostima; balans vode i elektrolita; natrijum hlorid; nosači lekova; putevi primene leka; plućni edem

ised administration of intravenous fluids is essential to maintain adequate circulating volume and organ perfusion [1].

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Abbreviations

IV fluids	– intravenous fluids
IFA	– International Fluid Academy
NICE	– National Institute for Health and Care Excellence
ERAS	– enhanced recovery after surgery
GIFTASUP	– Guidelines for Intravenous Fluid Therapy in Adult Surgical Patients
ICU	– Intensive Care Unit
SAPS II	– Simplified Acute Physiology Score
CCI	– Charlson Comorbidity Index

Concepts of rational fluid administration and fluid stewardship emphasise appropriate prescription and avoidance of fluid overload [2]. Perioperative and critical care fluid strategies are further guided by international recommendations such as the International Fluid Academy (IFA) consensus [3], as well as structured principles of fluid management including the “four D’s” and phases of fluid therapy [4], and classification into resuscitation, replacement, maintenance, and nutrition fluids [5].

Current perioperative fluid strategies are also defined by established guidelines such as ERAS, NICE, and GIFTASUP, which primarily emphasise resuscitation and maintenance fluids [6–8]. However, these frameworks do not sufficiently address less apparent sources of fluid administration, such as drug diluents and other ancillary fluids.

These additional inputs, collectively referred to as *fluid creep*, are intravenous (IV) fluids not prescribed for resuscitation or maintenance and include fluids used as medication vehicles, for line flushing, and for intravenous catheter maintenance. Although often considered negligible, they may significantly contribute to cumulative fluid and electrolyte load, particularly sodium and chloride, with potential clinical consequences such as fluid overload and tissue oedema [9–11].

Data on the contribution of fluid creep to postoperative electrolyte load in surgical Intensive Care Unit (ICU) patients remain limited. The primary aim of this study was to quantify fluid creep as a proportion of total intravenous fluid administration and to characterise the types of fluids contributing to it. The secondary aim was to assess its contribution to sodium and chloride load as well as its association with clinical signs of fluid overload.

Material and Methods

Study design and population

This prospective observational study was conducted at the University Clinical Center of Vojvodina, ICU, from February to April 2024. A total of 62 adult patients undergoing elective surgical procedures who required immediate postoperative ICU admission were assessed for eligibility. Patients were eligible for

inclusion if they required postoperative ICU stay for at least 48 hours. Nine patients were excluded from the study: two due to the need for renal replacement therapy, one due to death, four due to parenteral nutrition, and two because of an ICU stay shorter than 48 hours. Therefore, 53 patients were included in the final analysis.

The study was approved by the institutional Ethics Committee (No. 00-2012).

Data collection

Patient data were retrieved from medical records and the institutional electronic clinical information system.

Baseline data

Demographic data, surgical type, SAPS II score, and Charlson Comorbidity Index (CCI) were recorded.

Type and amount of intravenous fluids

The type and volume of IV fluids prescribed to each patient were retrieved from medical records. Data were collected on day 0 and postoperative day 1. Day 0 was defined as the day of the patient’s ICU admission (immediately following admission), and postoperative day 1 as the following day. All data were collected according to the research protocol. Each administered fluid was categorised as either a maintenance fluids or a fluid creep. Fluid creep was defined in this study as all non-resuscitation, non-maintenance intravenous fluids administered as drug diluents, carrier solutions, or for line flushing, including fluids co-administered with medications.

Sodium and chloride load calculation

Sodium and chloride loads were calculated by multiplying the administered volume for each IV fluid by the corresponding electrolyte concentrations reported by the manufacturer or previously published data [12].

Assessment of fluid overload

Peripheral oedema was assessed clinically by physical examination and recorded as present or absent. Lung ultrasound (LUS) was performed using a linear probe (6–12 MHz) to assess eight lung zones according to standardised protocols. B-lines were recorded in each zone, and the presence of more than three B-lines per zone was classified as pathological. Examinations were performed 24 hours and 48 hours after ICU admission [13].

Statistical analysis

Statistical analysis was performed using SPSS version 27, STATISTICA version 12, and Microsoft Excel. Descriptive statistics were used to summarise the data.

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range), depending on data distribution, while categorical variables were presented as frequencies and percentages. The primary outcome was the proportion of fluid creep in the total fluid intake. Secondary outcomes included sodium and chloride load, as well as clinical signs of fluid overload. Results were presented in tables and figures. A p-value < 0.05 was considered statistically significant.

Results

A total of 53 patients were included. Patient characteristics are presented in **Table 1**.

Most patients were male (66%), whereas females accounted for 34% (n = 18). Most patients (70%) were older than 65 years, with a mean age of 67.2 years (range, 44–77). The mean body mass index (BMI) was 25.63 kg/m².

Vascular surgery was performed in 68% of patients, while 32% underwent abdominal surgery. The mean SAPS II score was 30, and the median Charlson Comorbidity Index was 4.

Total daily fluid intake was 3971 $\pm$ 857 mL on day 0 and 3890 $\pm$ 731 mL on postoperative day 1 (p > 0.05) (**Table 2**).

The proportion of fluid creep was 19% on day 0 and 24% on postoperative day 1 (p > 0.05) (**Figure 1A**).

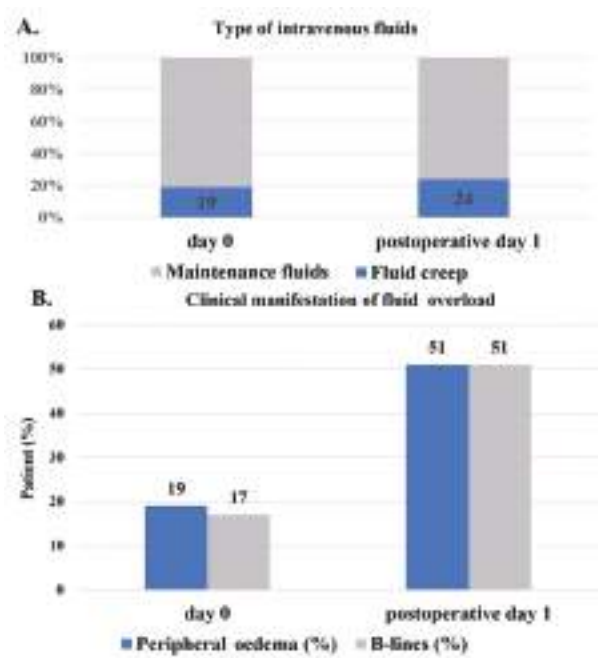


Figure 1. (A) Relative contribution of maintenance fluids and fluid creep on day 0 and postoperative day 1. (B) Changes in clinical parameters, including peripheral oedema and B-lines on lung ultrasound. Increased fluid creep was associated with worsening clinical findings.

Over the first 48 hours, fluid creep accounted for 21.6% of cumulative intravenous fluid intake.

Intravenous fluids administered as vehicles for medications accounted for the majority of fluid creep

Table 1. Demographic and clinical characteristics of patients

Demographic and clinical data (n=53)	
Male (n)	35 (66%)
Age (years)	Mean 67.2 (range 44-77)
BMI (kg/m ²)	25.63
Age > 65 years (n, %)	37 (70%)
Type of surgery (n,%)	Abdominal 17 (32%) Vascular 36 (68%)
SAPS II (points)	30
CCI (points)	5

Data are presented as mean values, numbers or percentages. body mass index; Simplified Acute Physiology Score; Charlson Comorbidity Index.

Table 2. Detailed fluid composition with fluid creep separately analysed as a distinct component of total intravenous fluid administration

Fluid composition	DAY 0 (mL, %)	POD 1 (mL, %)
Maintenance fluids IV	3216 (81%)	2956 (76%)
Fluid creep (total) IV	755 (19%)	934 (24%)
1. vehicles for IV medications	551 (73%)	645 (69%)
2. IV fluids co-administered with analgesics	204 (27%)	289 (31%)
Total IV fluids	3971 $\pm$ 857	3890 $\pm$ 731

Data are presented as mean values in millilitres and percentages. Total values are expressed as mean $\pm$ standard deviation in millilitres; DAY 0 – day of admission to the Intensive Care Unit, postoperative day 1.

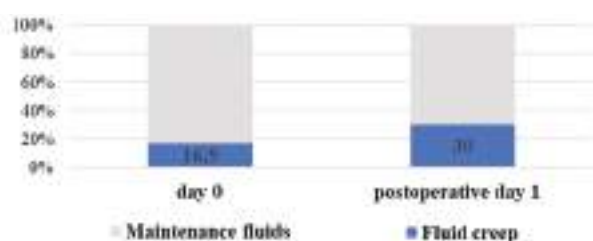


Figure 2. Relative contribution of fluid creep to total sodium and chloride load on day 0 and postoperative day 1

(73% and 69%, respectively), with 0.9% NaCl as the predominant diluent. The remaining proportion consisted of fluids co-administered with analgesics, including those that did not require dilution (**Table 2**).

On day 0, maintenance fluids were the primary source of sodium and chloride (83.1%), whereas fluid creep accounted for 16.9%. On postoperative day 1, the contribution of maintenance fluids decreased to 70%, while that of fluid creep increased to 30% of total electrolyte intake ($p < 0.05$) (**Figure 2**).

Peripheral oedema was present in 19% of patients on postoperative day 0 and in 51% on postoperative day 1 ($p < 0.05$). B-lines on lung ultrasound were observed in 17% of patients on postoperative day 0 and in 51% on postoperative day 1 ($p < 0.05$) (**Figure 1B**).

Discussion

This study suggests that fluid creep may represent a relevant and increasing component of postoperative fluid and electrolyte administration. Although total daily fluid intake did not change significantly between day 0 and postoperative day 1, the composition of administered fluids shifted, indicating that sources of fluid and electrolyte intake may be more important than total volume alone. Similar observations have been reported in other studies, where fluid creep has been shown to contribute significantly to overall intravenous fluid intake, highlighting its often under-recognised role in fluid management [14,15].

The observed increase in the contribution of fluid creep to electrolyte intake in our cohort (from 16.9% to 30%) further supports the concept that fluid creep is a dynamic and progressively important determinant of postoperative electrolyte load. These findings are in line with previous reports indicating that both maintenance fluids and fluid creep contribute substantially to sodium and chloride burden in hospitalised and critically ill patients [14–16].

The predominant use of 0.9% sodium chloride as a drug diluent likely contributed to the increased exposure to sodium and chloride observed in our patients. In our cohort, the majority of fluid creep originated from drug vehicle administration using

saline-based solutions. Although only a limited number of medications require saline dilution, its widespread use appears to be driven more by routine clinical practice than by strict necessity [17–19]. A practical approach to reducing unintended fluid and electrolyte loading from fluid creep involves more thoughtful selection and use of drug diluents. Instead of routinely used 0.9% sodium chloride, compatible alternatives such as 5% dextrose can be used to excess chloride and sodium intake significantly [20,21].

Additionally, the use of more concentrated drug preparations, when clinically appropriate, may reduce the volume of diluents required. Minimising the volumes used for drug infusions and catheter flushing, together with regular review of maintenance fluid prescriptions, may further help limit unnecessary fluid administration. Considering all sources of intravenous fluids in routine clinical practice could reduce fluid and electrolyte burden [15,16].

Importantly, the increase in fluid and electrolyte burden was accompanied by clinical signs of fluid accumulation. Excessive administration of sodium- and chloride-rich fluids may contribute to positive fluid balance, tissue oedema, pulmonary congestion, impaired organ function, and delayed recovery [10,11]. Raising awareness of hidden fluid sources and refining intravenous medication administration could be straightforward, cost-effective ways to manage fluids better and potentially improve patient outcomes. In our patients, peripheral oedema increased from 19% to 51% over 48 hours, while the prevalence of pathological B-lines on lung ultrasound increased from 17% to 51%.

B-lines on lung ultrasound are a sensitive marker of increased extravascular lung water. They may suggest pulmonary congestion in the appropriate clinical context, although they are not specific for fluid overload [21–23].

However, owing to the observational design of the study, causality between fluid creep and the observed clinical findings cannot be established, and the results should be interpreted as an association.

This study has several limitations, including a relatively small sample size and its observational design, which preclude establishing causal relationships between fluid creep and clinical outcomes at the individual patient level.

Conclusion

In this study, intravenous fluids used for drug dilution accounted for nearly one quarter of total intravenous fluid administration, representing a substantial and often under-recognised source of fluid and electrolyte load.

Fluid creep was identified as a clinically relevant and potentially modifiable contributor to perioperative fluid burden. Rational selection of diluent fluids may reduce sodium and chloride exposure and help

mitigate fluid-related complications in postoperative patients, and should be considered in perioperative fluid management protocols.

References

1. Edwards MR, Mythen MG. Fluid therapy in critical illness. *Extrem Physiol Med*. 2014;3:16.
 2. Wong A, Wilkinson J, Nasa P, Malbrain L, Malbrain MLNG. Introduction to fluid stewardship. In: Malbrain MLNG, Wong A, Nasa P, Ghosh S, editors. *Rational use of intravenous fluids in critically ill patients*. Cam: Springer; 2024. p. 547-65.
 3. Malbrain MLNG, Langer T, Annane D, Gattinoni L, Elbers P, Hahn RG, et al. Intravenous fluid therapy in the perioperative and critical care setting: executive summary of the International Fluid Academy (IFA). *Ann Intensive Care*. 2020;10(1):64.
 4. Malbrain MLNG, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. *Ann Intensive Care*. 2018;8(1):66.
 5. Malbrain MLNG, Mekeirele M, Raes M, Hendrickx S, Ghijselings I, Malbrain L, et al. The 4-indications of fluid therapy: resuscitation, replacement, maintenance and nutrition fluids, and beyond. In: Malbrain MLNG, Wong A, Nasa P, Ghosh S, editors. *Rational use of intravenous fluids in critically ill patients*. Cham: Springer; 2024. p. 167-202.
 6. Padhi S, Bullock I, Li L, Stroud M. Intravenous fluid therapy for adults in hospital: summary of NICE guidance. *BMJ*. 2013;347:f7073.
 7. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations: 2018. *World J Surg*. 2019;43(3):659-95.
 8. Soni N. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP): Cassandra's view. *Anaesthesia*. 2009;64(3):235-8.
 9. Santi M, Lava SA, Camozzi P, Giannini O, Milani GP, Simonetti GD, et al. The great fluid debate: saline or so-called "balanced" salt solutions? *Ital J Pediatr*. 2015;41(1):47.
 10. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care*. 2015;19(1):251.
 11. Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hopppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care*. 2012;16(5):R197.
 12. Tinawi M. New trends in the utilization of intravenous fluids. *Cureus*. 2021;13(4):e14619.
 13. Berry L, Rehnberg L, Groves P, Knight M, Stewart M, Dushianthan A. Lung ultrasound in critical care: a narrative review. *Diagnostics (Basel)*. 2025;15(6):755.
 14. Lee JW. Fluid and electrolyte disturbances in critically ill patients. *Electrolyte Blood Press*. 2010;8(2):72-81.
 15. Van Regenmortel N, Verbrughe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med*. 2018;44(4):409-17.
 16. Waskowski J, Salvato SM, Müller M, Hofer D, van Regenmortel N, Pfortmueller CA. Choice of creep or maintenance fluid type and their impact on total daily ICU sodium burden in critically ill patients: a systematic review and meta-analysis. *J Crit Care*. 2023;78:154403.
 17. Van Regenmortel N, Moers L, Langer T, Roelant E, De Weerd T, Caironi P, et al. Fluid-induced harm in the hospital: look beyond volume and start considering sodium. From physiology towards recommendations for daily practice in hospitalized adults. *Ann Intensive Care*. 2021;11(1):79.
 18. Trissel LA. Handbook on injectable drugs. 17th ed. Bethesda: American Society of Health-System Pharmacists; 2013. p. 1967-74.
 19. Sriram S, Aishwarya S, Moithu A, Sebastian A, Kumar A. Intravenous drug incompatibilities in the intensive care unit of a tertiary care hospital in India: are they preventable? *J Res Pharm Pract*. 2020;9(2):106-11.
 20. Bihari S, Prakash S, Potts S, Matheson E, Bersten AD. Addressing the inadvertent sodium and chloride burden in critically ill patients: a prospective before-and-after study in a tertiary mixed intensive care unit population. *Crit Care Resusc*. 2018;20(4):285-93.
 21. Veselinov V, Ivanov I, Dejanović J, Čelić D. Lung ultrasound in the assessment of hypervolemia in hemodialysis patients – two case reports. *Med Pregl*. 2018;71(5-6):187-90.
 22. Agricola E, Bove T, Oppizzi M, Marino G, Zangrillo A, Margonato A, et al. "Ultrasound comet-tail images": a marker of pulmonary edema: a comparative study with wedge pressure and extravascular lung water. *Chest*. 2005;127(5):1690-5.
 23. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012;8(4):577-91.
- Rad je primljen 2. V 2026.
Recenziran 3. VI 2026.
Prihvaćen za štampu 24. VI 2026.
BIBLID.0025-8105:(2026):LXXIX:7-8:169-173.

ASSOCIATION BETWEEN SERUM 25-HYDROXYVITAMIN D CONCENTRATIONS AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPENIA AND OSTEOPOROSIS

POVEZANOST SERUMSKIH KONCENTRACIJA 25-HIDROKSIVITAMINA D I MINERALNE GUSTINE KOSTIJU KOD ŽENA U POSTMENOPAUZI SA OSTEOPENIJOM I OSTEOPOROZOM

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Originalni naučni rad

UDK 616.71-007.233/.234:616.391.6

<https://doi.org/10.2298/MPNS2608174M>

Abstract

Introduction. Vitamin D regulates approximately 3% of the human genome, which helps explain its roles in the musculoskeletal, cardiovascular, and immune systems, as well as in the development of malignant diseases and diabetes. Its deficiency may cause rickets in children and osteomalacia and osteoporosis in adults. Every 3 seconds, an osteoporotic fracture occurs, affecting 1 in 3 women and 1 in 5 men over the age of 50 years. The study aimed to evaluate serum vitamin D concentrations in postmenopausal women with osteopenia and osteoporosis and to assess the association between vitamin D status and bone mineral density. **Material and Methods.** This retrospective study included medical records of 100 postmenopausal women diagnosed with osteopenia or osteoporosis by dual-energy X-ray absorptiometry. Participants were divided into three groups by serum 25-hydroxyvitamin D concentrations (< 50 nmol/L; 50–75 nmol/L; ≥ 75 nmol/L) and four age groups (≤ 49; 50–59; 60–69; ≥ 70 years). **Results.** The mean age of the participants was 67.14 years. The mean 25-hydroxyvitamin D concentration was 50.28 nmol/L in women with osteoporosis and 54.98 nmol/L in women with osteopenia. A statistically significant positive correlation was observed between 25-hydroxyvitamin D concentration and hip bone mineral density. **Conclusion.** Serum vitamin D concentrations in postmenopausal women with osteopenia and osteoporosis were below the desirable range. A positive and statistically significant correlation was found between serum vitamin D concentration and hip bone mineral density. Older age was associated with a higher prevalence of fractures among women with osteopenia and osteoporosis.

Key words: Bone Diseases, Metabolic; Osteoporosis; Osteoporosis, Postmenopausal; Vitamin D; Vitamin D Deficiency; Bone Density

Sažetak

Uvod. Vitamin D je potentni regulator funkcije oko 3% ljudskog genoma, čime se objašnjava njegova uloga u funkciji koštano-mišićnog sistema, imunoprocesima, kardiovaskularnom sistemu, ali i razvoju malignih bolesti i dijabetesa. Deficijencija ovog vitamina može usloviti rahitis kod dece, osteomalaciju i osteoporozu kod odraslih. Svake tri sekunde nastaje jedna osteoporotična fraktura koju pretrpi svaka treća žena i svaki peti muškarac stariji od 50 godina. Cilj rada bio je da se odrede serumske koncentracije vitamina D kod žena sa osteoporozaom i osteopenijom, te utvrdi postojanje korelacije između serumskih koncentracija vitamina D i mineralne gustine kosti. **Materijal i metode.** Sprovedena je retrospektivna analiza istorija bolesti 100 žena u postmenopauzi kod kojih je metodom dvostruke rendgenske apsorpcijometrije postavljena dijagnoza osteopenije ili osteoporoze. Ispitanice su na osnovu vrednosti 25-hidroksi vitamina D podeljene u tri grupe (< 50 nmol/L; 50–75 nmol/L; ≥ 75 nmol/L), a prema starosti u četiri grupe (≤ 49; 50–59; 60–69; ≥ 70). **Rezultati.** Prosečna starost ispitanica iznosila je 67,14 godina. Prosečna vrednost 25-hidroksi vitamina D kod ispitanica sa osteoporozaom iznosila je 50,28 nmol/L, a kod ispitanica sa osteopenijom 54,98 nmol/L. Uočena je statistički značajna pozitivna korelacija između 25-hidroksi vitamina D i mineralne gustine kosti kuka. **Zaključak.** Serumske koncentracije vitamina D kod žena u postmenopauzi sa osteopenijom i osteoporozaom su ispod opsega poželjnih vrednosti. Postoji pozitivna i statistički značajna korelacija između serumske koncentracije vitamina D i mineralne gustine kosti kuka. Starija životna dob bila je povezana sa većom učestalošću preloma kod žena sa osteopenijom i osteoporozaom.

Ključne reči: metaboličke bolesti kostiju; osteoporoza; postmenopauzalna osteoporoza; vitamin D; nedostatak vitamina d; gustina kostiju

Introduction

Vitamin D, often referred to as the “hormone of the future” with basic structure consists of four cho-

lesterol rings, has been recognised as a potent regulator of approximately 3% of the human genome. This supports its role in the musculoskeletal system, immune processes, cardiovascular function, and the

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Abbreviations

D2	– ergocalciferol
D3	– cholecalciferol
25(OH)D	– 25-hydroxyvitamin D
1,25(OH) ₂ D	– 1,25-dihydroxyvitamin D (calcitriol)
DBP	– vitamin D-binding protein
VDR	– vitamin D receptor
IL	– interleukin
TNF-α	– tumour necrosis factor alpha
M-CSF	– macrophage colony-stimulating factor
PTH	– parathyroid hormone
GH	– growth hormone
IGF-1	– insulin-like growth factor 1
DEXA	– dual-energy X-ray absorptiometry
BMD	– bone mineral density
SD	– standard deviation
CMIA	– chemiluminescent microparticle immunoassay
ANOVA	– analysis of variance

development of malignant diseases and diabetes [1]. Several forms of vitamin D are known today, but only ergocalciferol (D2) and cholecalciferol (D3) exert significant physiological effects in humans. Dietary sources include foods of animal origin (D3) and plant origin (D2), while most is majority is synthesised by exposure of 7-dehydrocholesterol to ultraviolet radiation (290–315 nm), forming previtamin D3, which is subsequently converted by thermal isomerisation into cholecalciferol (D3).

Following the synthesis of vitamin D3 in the skin, it undergoes its first transformation in the liver to 25-hydroxycholecalciferol (25(OH)D) by the action of the enzyme 25-hydroxylase [2]. The resulting 25(OH)D, or calcidiol, represents the circulating metabolite whose laboratory measurement reflects vitamin D stores in the body. The second hydroxylation occurs predominantly in the kidneys under the influence of 1α-hydroxylase, resulting in the formation of 1,25-dihydroxycholecalciferol (1,25(OH)₂D), or calcitriol. In addition to renal cells, endothelial cells, pancreatic cells, pulmonary cells, parathyroid gland cells, and many others also express 1α-hydroxylase and can locally synthesise vitamin D for their own needs. After synthesis, calcitriol binds to vitamin D-binding protein (DBP) in the plasma and is transported to all cells that express the vitamin D receptor (VDR).

Vitamin D exerts its primary role through participation in osteogenesis and maintenance of bone structural integrity by regulating calcium and phosphorus homeostasis and stimulating their intestinal absorption and reabsorption in the proximal renal tubules. In addition, vitamin D represents an important component of the immune system, as recent studies have also attributed antiproliferative properties to it [3]. It is estimated that 47% of the global population has vitamin D deficiency [4]. The two most common causes of vitamin D deficiency are

inadequate dietary intake and insufficient sun exposure, which largely depend on geographical latitude. Countries of the Balkan Peninsula are located above the 35th parallel, where reduced endogenous vitamin D synthesis has been documented during the autumn and winter months [5,6]. Deficiency of this vitamin may result in numerous disorders, including rickets in children, osteomalacia and osteoporosis in adults, hyperparathyroidism, and various disturbances of the nervous, muscular, immune, and glucose-regulating systems [3]. Osteoporosis is a chronic, progressive metabolic skeletal disorder characterised by reduced bone mass and deterioration of bone microarchitecture [7,8]. The principal pathophysiological mechanism of osteoporosis is accelerated overall bone turnover with an imbalance between bone formation and bone resorption in favour of the latter. Trabecular bone is metabolically the most active, and therefore, bone loss is initially observed in the lumbar vertebrae, proximal femur, and wrist region [3].

Osteoporosis may be classified in several ways, although the most widely accepted classification is the aetiological division into primary and secondary osteoporosis. Primary osteoporosis includes idiopathic and involutional osteoporosis, the latter is further divided into postmenopausal and senile osteoporosis. Postmenopausal osteoporosis (Type I) is the most common form of the disease and occurs in women during the postmenopausal period up to the age of 70 years [9]. Oestrogen deficiency resulting from natural or artificial menopause leads to increased production of inflammatory cytokines (IL-6, IL-1, IL-11, TNF-α, M-CSF) and enhanced sensitivity of osteoblast and osteoclast precursor cells to their effects, thereby increasing osteoclast activity in the absence of the modulatory effects of hormones and growth factors (calcitonin, PTH, GH, IGF-1). During the early postmenopausal period, accelerated bone remodelling, with a predominance of bone resorption, disrupts trabecular microarchitecture. Simultaneously, reduced periosteal apposition and increased endocortical resorption impair cortical microarchitecture, leading to vertebral and distal forearm fractures. An osteoporotic fracture is defined as a fracture occurring spontaneously or after minimal trauma [10,11].

Involutional osteoporosis (Type II) occurs in older women and men after age of 70. Its pathogenesis is associated with physiological ageing processes, including reduced calcium absorption, decreased calcitriol synthesis, and increased PTH secretion. It is characterised by the loss of both trabecular and cortical bone [11,12]. Secondary osteoporosis develops as a consequence of underlying diseases (e.g., Cushing's syndrome, diabetes mellitus, cystic fibrosis) or chron-

ic use of medications (corticosteroids, antiepileptic drugs) that affect bone metabolism [9].

The gold standard for assessing bone mineral density and diagnosing of osteoporosis is dual-energy X-ray absorptiometry (DEXA) of the lumbar spine (L1–L4) and hip. Bone mineral density (BMD) is expressed in g/cm^2 and reported using T-scores and Z-scores. The T-score represents the deviation of measured bone mass from the average peak bone mass of young adults, whereas the Z-score represents the deviation from the expected average for individuals of the same age. Osteoporosis is diagnosed when the T-score is ≤ -2.5 SD, whereas osteopenia is defined as a T-score between -2.5 and -1.0 SD. Severe osteoporosis is defined as a T-score ≤ -2.5 accompanied by one or more fragility fractures. The T-score is used to assess bone density in postmenopausal women and men older than 50 years, whereas the Z-score is applied in younger individuals and premenopausal women. Osteoporosis treatment includes both non-pharmacological measures (lifestyle modification, reduction of risk factors, calcium and vitamin D supplementation) and pharmacological therapy consisting of two main groups of medications: antiresorptive agents (bisphosphonates, selective oestrogen receptor modulators, hormone replacement therapy, calcitonin, and denosumab) and anabolic agents (teriparatide, abaloparatide, and romosozumab) [8,13].

Reduced endogenous vitamin D synthesis, specifically a decrease in the concentration of its active metabolite, also plays an important role in the pathophysiology of osteoporosis, making bone more susceptible to fractures [12,14].

This study aimed to determine serum 25-hydroxyvitamin D [25(OH)D] concentrations in women with osteopenia and osteoporosis, and to assess the association between serum 25(OH)D concentrations and bone mineral density (BMD).

Material and Methods

This study was a retrospective analysis of medical records from 100 female patients treated on an outpatient basis at the Clinic for Endocrinology, Diabetes, and Metabolic Disorders. Medical records were selected from the clinic archive according to predefined inclusion and exclusion criteria, without restriction to a predefined calendar period. Approval for the study was obtained from the Clinic and the Ethics Committee of the University Clinical Center of Vojvodina.

The study included postmenopausal women diagnosed with osteopenia or osteoporosis based on DXA examination and with available serum vitamin D measurements obtained before the initiation of any

treatment. Women with secondary osteoporosis were excluded from the study. The following data were collected from medical records: demographic characteristics (age), serum 25-hydroxyvitamin D [25(OH)D] concentrations, history of fractures, and bone mineral density measurements (T-score).

Bone mineral density of the lumbar spine (L1–L4) and hip was assessed using a Lunar densitometer. T-scores and Z-scores were calculated using the device software. Osteopenia was defined as a T-score between -1.0 and -2.5 , whereas osteoporosis was defined as a T-score ≤ -2.5 . Serum vitamin D concentrations, specifically its circulating metabolite 25(OH)D, were measured using the chemiluminescent microparticle immunoassay (CMIA) method on an automated Abbott Alinity immunoassay analyser. Values equal to or above 75 nmol/L were considered sufficient, values between 50 and 75 nmol/L were classified as insufficient, and values below 50 nmol/L as vitamin D deficiency. Participants were stratified into four age groups (≤ 49 years, 50–59 years, 60–69 years, and ≥ 70 years) and into three groups according to serum 25(OH)D concentration (≥ 75 nmol/L, 50–75 nmol/L, and < 50 nmol/L).

Continuous variables were described using minimum and maximum values, means, and standard deviations. Categorical variables were expressed as percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test. Differences in mean values between groups were evaluated using analysis of variance (ANOVA). Associations between continuous variables were assessed using Pearson's correlation coefficient. Statistical analyses were performed using the R statistical software package (version 4.4.0), with statistical significance set at $p \leq 0.05$.

Results

The study included 100 women diagnosed with osteopenia or osteoporosis based on DXA examination. Demographic and clinical characteristics of the study population are presented in **Table 1**. The mean age of the participants was 67.14 years, while the mean serum vitamin D concentration was 51.69 nmol/L. The mean lumbar spine (L1–L4) T-score was -2.51 . The mean hip T-score was -1.95 , which was 0.56 higher than the lumbar spine T-score. The lowest recorded T-score was -4.5 at the hip and -4.8 at the lumbar spine.

Participants were stratified into four age groups: ≤ 49 years, 50–59 years, 60–69 years, and ≥ 70 years (**Table 2**). The largest group consisted of women aged 70 years and older ($n = 45$), followed by those aged 60–69 years ($n = 40$). Eight participants were between 50 and 59 years of age, while only seven were young-

Table 1. Demographic and Clinical Data

Variable	Mean	SD	MIN	
Age (years)	67.14	9.04	41	83
25(OH)D (nmol/L)	51.69	21.08	10	98
L1-L4 T-score (SD)	-2.51	0.82	-4.8	-0.6
Hip T-score (SD)	-1.95	0.94	-4.5	0.4

Table 2. Baseline Characteristics of the Study Sample

Variable	Category	n	
Age (years)	≤ 49	7	7
	50-59	8	8
	60-69	40	40
	≥70	45	45
Fractures	Yes	47	47
	No	53	53
25(OH)D (nmol/L)	<50	45	45
	50-75	40	40
	≥75	15	15
T-score (BMD classification)	Osteopenia	30	30
	Osteoporosis	70	70

Table 3. Mean age, history of fractures, serum 25(OH)D concentrations, and bone mineral density in women with osteopenia and osteoporosis

	Age (years) (Mean ±SD)	Fractures, n	25(OH)D (nmol/L) (Mean±SD)	Hip BMD (g/cm ²) (Mean± SD)	L1-L4 BMD (g/cm ²) (Mean±SD)
Osteopenia	67.30 ± 8.61	10	54.98 ± 20.79	0.848 ± 0.07	0.967 ± 0.05
Osteoporosis	67.07 ± 9.28	37	50.28 ± 21.19	0.729 ± 0.10	0.834 ± 0.10

er than 50 years. Based on serum 25(OH)D concentrations, participants were categorised into three groups: <50 nmol/L, 50–75 nmol/L, and ≥75 nmol/L. Only 15 participants had serum 25(OH)D concentrations within the desirable range (≥75 nmol/L). The remaining participants had suboptimal vitamin D status, with 40 exhibiting vitamin D insufficiency (50–75 nmol/L) and 45 exhibiting vitamin D deficiency (<50 nmol/L). According to T-scores measured at the hip and lumbar spine, participants were classified into two groups: osteopenia (n = 30) and osteoporosis (n = 70). A history of fracture was reported in 47% of the participants.

As shown in **Table 3**, women with osteoporosis had lower mean serum vitamin D concentrations (50.28 nmol/L), lower hip BMD values (0.729 g/cm²), and lower lumbar spine (L1–L4) BMD values (0.834 g/cm²) compared with women with osteopenia, whose corresponding mean values were 54.98 nmol/L, 0.848 g/cm², and 0.967 g/cm², respectively. In addition, fractures were more common among women with osteoporosis, with 37 participants reporting a history of fracture.

By age group, the lowest mean serum vitamin D concentration was observed in women aged 70 years

and older (48.23 nmol/L), whereas the highest was found in women younger than 50 years (60.71 nmol/L). Although there was a tendency of lower mean serum vitamin D concentration with increasing age, the differences between age groups were not statistically significant (p = 0.146). Women with a history of fractures had the lowest mean serum vitamin D concentration (49.06 nmol/L), whereas those without fractures had a mean concentration approximately 5 nmol/L higher. However, this difference was not statistically significance (p = 0.242). Participants with osteopenia had slightly higher mean serum vitamin D concentrations (54.98 nmol/L) than those with osteoporosis (50.28 nmol/L); however, the difference was not statistically significant (p = 0.310) (**Table 4**).

The mean age of participants with a history of fracture was 69.51 years, compared with 65.03 years among those without a history of fracture. This difference was statistically significant (p = 0.013).

The mean age of participants with sufficient vitamin D concentrations (≥75 nmol/L) was 65.66 years, whereas the mean age was higher among those with suboptimal vitamin D status, reaching 67.47 years in the vitamin D insufficiency group (50–75 nmol/L)

Table 4. Mean serum 25(OH)D concentrations in subjects in relation to age, presence of fractures, and bone mineral density

	Category	n	Mean $\pm$ SD	
Age (years)	≤ 49	7	60.71 $\pm$ 26.08	0.146
	50-59	8	49.91 $\pm$ 17.99	
	60-69	40	54.36 $\pm$ 19.58	
	≥ 70	45	48.23 $\pm$ 21.99	
Fractures	Yes	47	49.06 $\pm$ 22.66	0.242
	No	53	54.02 $\pm$ 19.49	
BMD (g/cm ²) (classification)	Osteopenia	30	54.98 $\pm$ 20.79	0.310
	Osteoporosis	70	50.28 $\pm$ 21.19	

Table 5. Mean age in relation to serum 25(OH)D concentrations, presence of fractures, and bone mineral density

	Category	n	Mean $\pm$ SD	
Fractures	Yes	47	69.51 $\pm$ 7.34	0.013
	No	53	65.03 $\pm$ 9.93	
25(OH) (nmol/L)	<50	45	67.33 $\pm$ 9.66	0.793
	50-75	40	67.47 $\pm$ 7.30	
	≥ 75	15	65.66 $\pm$ 11.58	
BMD (g/cm ²) (classification)	Osteopenia	30	67.3 $\pm$ 8.61	0.909
	Osteoporosis	70	67.07 $\pm$ 9.28	

Table 6. Correlation between 25(OH)D concentration and bone mineral density (BMD) (N = 100)

Correlation	r	
25(OH)D vs. L1-L4 BMD	0.17	0.07
25(OH)D vs. Hip BMD	0.19	0.05

r - Pearson correlation coefficient; *p* - statistical significance of the correlation ($p \leq 0.05$)

and 67.33 years in the vitamin D deficiency group (<50 nmol/L). Although lower vitamin D concentrations were observed with increasing age, the differences were not statistically significant ($p = 0.793$). Similarly, no significant difference in age was observed between participants with osteopenia and those with osteoporosis. The mean age was 67.30 years in the osteopenia group and 67.07 years in the osteoporosis group ($p = 0.909$) (Table 5).

Pearson's correlation analysis was performed to evaluate the association between serum vitamin D concentrations and bone mineral density at the hip and lumbar spine (L1-L4) (Table 6). A positive correlation was observed between serum vitamin D concentration and lumbar spine BMD; however, the association did not reach statistical significance ($r = 0.17$, $p = 0.07$). Similarly, a weak positive correlation was observed between serum vitamin D concentration and hip BMD, which was statistically significant ($r = 0.19$, $p = 0.05$).

Discussion

Physical inactivity, a sedentary lifestyle, and numerous metabolic disorders contribute to adverse changes in the skeletal system. Today, the prevalence

of non-communicable diseases continues to increase, with osteoporosis representing not only a major health concern but also a significant socioeconomic burden [15]. Age is an important biological determinant of bone loss. Peak bone mass is estimated to be achieved by the age of 25 years, after which bone density gradually declines, with an average decrease of approximately 0.5% every four years in adulthood. Furthermore, bone mineral density loss is two to three times greater in women after menopause [16]. In a study conducted by Labronici et al., the mean age of women diagnosed with osteopenia was 69 years, whereas women with osteoporosis were older, with a mean age of 75 years. The authors reported a statistically significant difference in age between women with osteoporosis and those with osteopenia [17]. Similar findings have been reported in more recent population-based studies, which demonstrated that the prevalence of osteopenia and osteoporosis increases significantly with age, particularly among individuals older than 70 years [18]. In our study, the mean age of women with osteopenia was 67 years, while women with osteoporosis were of a similar age. Consequently, no statistically significant difference was observed between these groups. One possible

explanation is that our study did not include women with normal bone mineral density and was conducted on a relatively small sample.

The role of vitamin D as a key factor in maintaining skeletal health has received increasing attention in recent years. A decline in serum vitamin D concentrations has been observed across all age groups over recent decades. Previous studies have shown that vitamin D deficiency is more prevalent in women than in men, particularly among older women with osteopenia and osteoporosis [19].

In our study, the mean serum vitamin D concentration was 54.98 nmol/L in women with osteopenia and 50.28 nmol/L in women with osteoporosis. Although the difference was not statistically significant, both groups exhibited vitamin D concentrations below the recommended range. Similar findings were reported in a Brazilian study by Labronici et al., where mean vitamin D concentrations were 54 nmol/L in women with osteopenia and 55 nmol/L in women with osteoporosis. Likewise, no significant difference was observed between the two groups [17]. In contrast, Laktašić et al. reported somewhat lower mean serum vitamin D concentrations in women with osteopenia (48 nmol/L) and osteoporosis (45 nmol/L) [20]. These lower concentrations were observed in women with a mean age of approximately 60 years, which differs from our findings, where comparable vitamin D concentrations were recorded primarily among women older than 70 years.

Considering the geographical latitude and the greater number of sunny days, higher vitamin D concentrations might be expected among women from Brazil than among women from the Balkan region. However, substantial differences were not observed. This finding suggests that endogenous vitamin D synthesis depends not only on sunlight exposure but also on factors such as lifestyle, body mass index, dietary intake, and chronic diseases. This observation is consistent with contemporary epidemiological data demonstrating a high global prevalence of vitamin D deficiency, even in regions with abundant sunlight [4].

Numerous studies have investigated the relationship between vitamin D and bone mineral density. Malavolta et al. conducted a study among postmenopausal women in Italy. They reported a strong positive correlation between serum vitamin D concentrations and bone mineral density at both the hip and lumbar spine [21]. Laktašić et al. demonstrated a positive correlation only between vitamin D concentration and hip bone mineral density [20]. Similarly, our study identified a weak positive correlation between serum 25(OH)D concentration and hip bone mineral density that was statistically significant, whereas the cor-

relation with lumbar spine bone mineral density was also weak and positive but did not reach statistical significance. In contrast, Garnero et al. found no association between vitamin D concentrations and bone mineral density at either the hip or the spine [22]. These heterogeneous findings are likely explained by differences in ethnicity, age distribution, study design, and the fact that vitamin D deficiency represents only one of several factors contributing to reduced bone mineral density. In addition to age and female sex, decreased bone mineral density is influenced by oestrogen deficiency, physical inactivity, inadequate sun exposure, smoking, low body mass index, and numerous other factors. Previous studies have shown that women with five or more risk factors have up to a 17-fold higher incidence of hip fractures [23]. Furthermore, hip fractures are associated with mortality of up to 36% during the first year after fracture [16].

Osteoporosis represents a major global health challenge. It is estimated to cause nearly 8.9 million fractures worldwide annually. An osteoporotic fracture occurs every 3 seconds, affecting 1 in 3 women and 1 in 5 men over the age of 50 years [15]. In our study, 47% of participants had a history of fracture. The mean age of women with fractures was 69 years, whereas women without fractures were approximately four years younger. This difference was statistically significant. The importance of age as a risk factor for fractures was also demonstrated by Labronici et al., who reported a mean age of 75 years among women with fractures, six years older than the women in our cohort. However, the prevalence of fractures in their study was lower (25%) [17]. Similar findings have been reported in more recent population-based and cohort studies, indicating that the risk of osteoporotic fractures increases exponentially after the age of 65 years, with a further increase after the age of 70 years, regardless of geographic region or ethnicity [24]. Although our study did not demonstrate a statistically significant difference, mean vitamin D concentrations were lower among women with fractures (49 nmol/L) than among those without fractures (54 nmol/L). Fisher et al. similarly reported a high prevalence of vitamin D deficiency among women with fractures, with vitamin D insufficiency present in nearly 80% of hip fracture cases [25]. Comparable findings were reported in a recent meta-analysis by Lv et al., which demonstrated a dose-dependent association between lower serum 25(OH)D concentrations and an increased risk of hip and non-vertebral fractures, particularly among older women [26].

Numerous studies emphasise the importance of early vitamin D and calcium supplementation for fracture prevention. Larsen et al. reported that individuals

older than 65 years receiving vitamin D supplementation at doses greater than 400 IU/day had a 16% lower fracture risk [27]. However, vitamin D supplementation should be used with caution. Sanders et al. demonstrated that very high annual doses of vitamin D (500,000 IU once yearly for five years) administered to women aged 70 years and older paradoxically increased fracture risk [28]. More recent meta-analyses and randomised controlled trials have shown that vitamin D supplementation alone does not significantly reduce fracture risk in the general population. Any potential benefit on bone mineral density appears to be modest and is most consistently observed when vitamin D is administered in combination with calcium [29]. These findings further emphasise the importance of comprehensive osteoporosis assessment and the timely identification of modifiable risk factors in routine clinical practice [30].

Limitations

Several limitations of this study should be acknowledged. First, its retrospective design, relatively small sample size, and single-centre setting may limit

the generalisability of the findings. In addition, several factors that may influence vitamin D status and bone mineral density, including body mass index, physical activity, and dietary habits (particularly calcium and vitamin D intake), were not evaluated. Future large-scale prospective studies are needed to clarify further the relationship between vitamin D status and bone mineral density in postmenopausal women.

Conclusion

Our study confirmed that postmenopausal women with osteopenia or osteoporosis have serum vitamin D concentrations below the recommended range. A weak positive correlation between serum 25-hydroxyvitamin D concentration and hip bone mineral density was statistically significant, whereas the weak positive correlation with lumbar spine bone mineral density did not reach statistical significance. Increasing age was associated with a higher prevalence of fractures among women with osteopenia and osteoporosis.

References

1. Bielen L, Žagar I. *Alfakalcidol. Medicus.* 2015;24(2):183-90.
2. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr.* 2012;95(6):1357-64.
3. Zappulo F, Cappuccilli M, Cingolani A, Scrivo A, Chiocchini ALC, Nunzio MD, et al. Vitamin D and the kidney: two players, one console. *Int J Mol Sci.* 2022;23(16):9135.
4. Dunlop E, Pham NM, Van Hoang D, Mazahery H, Neo B, Shrapnel J, et al. A systematic review and meta-analysis of circulating 25-hydroxyvitamin D concentration and vitamin D status worldwide. *J Public Health (Oxf).* 2025;47(4):e520-9.
5. Alshishtawy MM. Vitamin D deficiency: this clandestine endemic disease is veiled no more. *Sultan Qaboos Univ Med J.* 2012;12(2):140-52.
6. Bandeira F, Griz L, Dreyer P, Eufrazino C, Bandeira C, Freese E. Vitamin D deficiency: a global perspective. *Arq Bras Endocrinol Metabol.* 2006;50(4):640-6.
7. Leidig-Bruckner G, Raue F, Frank-Raue K. Secondary osteoporosis: relevant clinical characteristics in diagnosis and therapy. *Dtsch Med Wochenschr.* 2012;137(7):326-32.
8. Zvekić-Svorcan J, Bošković K, Janković T, Krasnik R, Igić N, Minaković I. Diagnosis of osteoporosis and prevention of osteoporotic fractures. *Med Pregl.* 2022;75(Suppl 2):13-8.
9. Amarnath SS, Kumar V, Das SL. Classification of osteoporosis. *Indian J Orthop.* 2023;57(Suppl 1):49-54.
10. Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. *Chronic Dis Transl Med.* 2015;1(1):9-13.
11. Becker C. Pathophysiology and clinical manifestations of osteoporosis. *Clin Cornerstone.* 2006;8(1):19-27.
12. Veldurthy V, Wei R, Oz L, Dhawan P, Jeon YH, Christakos S. Vitamin D, calcium homeostasis and aging. *Bone Res.* 2016;4:16041.
13. Morin SN, Leslie WD, Schousboe JT. Osteoporosis: a review. *JAMA.* 2025;334(10):894-907.
14. Cong B, Zhang H. The effects of combined calcium and vitamin D supplementation on bone mineral density and fracture risk in postmenopausal women with osteoporosis: a systematic review and meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord.* 2025;26(1):928.
15. Bruyère O, Scott D, Papaioannou A, Buehring B, Camargos BM, Chapurlat R, et al. The impact of sedentary behavior and physical activity on bone health: a narrative review from the Rehabilitation Working Group of the International Osteoporosis Foundation. *Calcif Tissue Int.* 2025;116(1):109.
16. Hendrickx G, Boudin E, Van Hul W. A look behind the scenes: the risk and pathogenesis of primary osteoporosis. *Nat Rev Rheumatol.* 2015;11(8):462-74.
17. Labronici PJ, Blunck SS, Lana FR, Esteves BB, Franco JS, Fukuyama JM, et al. Vitamin D and its relation to bone mineral density in postmenopausal women. *Rev Bras Ortop.* 2013;48(3):228-35.
18. Fan Y, Li Q, Liu Y, Miao J, Zhao T, Cai J, et al. Sex- and age-specific prevalence of osteopenia and osteoporosis: a sampling survey. *JMIR Public Health Surveill.* 2024;10:e48947.
19. Chen X, Shen L, Gao C, Weng R, Fan Y, Xu S, et al. Vitamin D status and its associations with bone mineral density, bone turnover markers, and parathyroid hormone in Chinese postmenopausal women with osteopenia and osteoporosis. *Front Nutr.* 2024;10:1307896.
20. Laktašić-Žerjavić N, Rukavina K, Babić-Naglić Đ, Čurković B, Anić B, Soldo-Jureša D. Povezanost statusa vitamina D s mineralnom gustoćom kosti u hrvatskih žena u postmenopauzi. *Reumatizam.* 2013;60(1):8-13.
21. Malavolta N, Pratelli L, Frigato M, Mule R, Mascia ML, Gnudi S. The relationship of vitamin D status to bone mineral density in an Italian population of postmenopausal women. *Osteoporos Int.* 2006;16(12):1691-7.

22. Garnero P, Munoz F, Sornay-Rendu E, Delmas PD. Associations of vitamin D status with bone mineral density, bone turnover, bone loss and fracture risk in healthy postmenopausal women. The OFELY study. *Bone*. 2007;40(3):716-22.

23. World Health Organization Scientific Group. Assessment of osteoporosis at the primary health care level [Internet]. Geneva: World Health Organization; 2007 [cited 2026 Feb 12]. Available from: https://www.fraxplus.org/sites/frax/files/pdf/WHO_Technical_Report.pdf

24. GBD 2019 Fracture Collaborators. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet Healthy Longev*. 2021;2(9):e580-92.

25. Fisher A, Srikusalanukul W, Davis M, Smith P. Hip fracture type: important role of parathyroid hormone (PTH) response to hypovitaminosis D. *Bone*. 2010;47(2):400-7.

26. Lv QB, Gao X, Liu X, Shao ZX, Xu QH, Tang L, et al. The serum 25-hydroxyvitamin D levels and hip fracture risk: a meta-analysis of prospective cohort studies. *Oncotarget*. 2017;8(24):39849-58.

27. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *J Bone Miner Res*. 2004;19(3):370-8.

28. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815-22.

29. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(12):e1917789.

30. Matijević R. Osteoporosis – treatment gap. *Med Pregl*. 2022;75(Suppl 2):19-21.

Rad je primljen 11. VI 2026.

Recenziran 3. VIII 2026.

Prihvaćen za štampu 3. VIII 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:174-181.

THE INFLUENCE OF THE FIRST CHILDBIRTH ON THE OCCURRENCE OF STRESS URINARY INCONTINENCE AND SEXUAL DYSFUNCTION

UTICAJ PRVOG POROĐAJA NA POJAVU STRES-URINARNE INKONTINENCIJE I SEKSUALNE DISFUNKCIJE

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Original study
Originalni naučni rad
UDK 618.4:159.922.1

UDK 618.4:616.62-008.22

<https://doi.org/10.2298/MPNS2608183L>

Abstract

Introduction. Urinary incontinence is a very common pelvic floor disorder defined as the “complaint of involuntary loss of urine”. Sexual dysfunction prevents a person from experiencing pleasure during sexual activities. The research aimed to analyse the frequency of urinary incontinence and sexual dysfunction in female subjects 6 to 18 months after the first delivery and the association with factors at delivery. **Material and Methods.** The research included 69 respondents. The inclusion criteria was one previous term birth within 6-18 months. A survey created with Google Forms was used to collect data. **Results.** Sexual dysfunction was reported by 21/69 (30%) respondents, and urinary incontinence by 8/69 (12%). Urinary incontinence was significantly more common among subjects with obstetric soft tissue lacerations ($p < 0.01$). Negative emotional reactions during sexual intercourse were more frequent in respondents with a longer period since childbirth ($p < 0.001$). Only 3/21 (14%) subjects with sexual dysfunction and 3/8 (38%) with urinary incontinence reported the problem to their doctor. The doctor asked 16/69 (23%) about the problem of urinary incontinence during a regular visit, and about sexual dysfunction in 15/69 (22%) of the respondents. **Conclusion.** Sexual dysfunction and urinary incontinence are common conditions after the first childbirth. Trauma of the birth canal during childbirth may contribute to urinary incontinence after delivery. Negative emotional reactions increase during the time that passes after childbirth. Patients and doctors rarely discuss sexual dysfunction and urinary incontinence. **Key words:** Urinary Incontinence; Sexual Dysfunction, Physiological; Parturition; Delivery, Obstetric; Obstetric Labor Complications; Postpartum Period; Pelvic Floor Disorders; Psychological Distress; Emotions

Introduction

The pelvic floor is composed of muscles, ligaments, and fascia. The coordinated function of these structures is essential for maintaining pelvic girdle stability and muscle tone, as well as for continence and sexual

Sažetak

Uvod. Urinarna inkontinencija je veoma rasprostranjen poremećaj karličnog dna koji se definiše kao „žalba na nevoljni gubitak urina“. Seksualna disfunkcija sprečava osobu da doživi zadovoljstvo prilikom seksualne aktivnosti. Cilj ovog istraživanja bio je da se ispita učestalost urinarne inkontinencije i seksualne disfunkcije kod ženskih ispitanica šest do 18 meseci nakon prvog porođaja i povezanost sa faktorima na porođaju. **Materijal i metode.** Istraživanje je obuhvatilo 69 ispitanica. Kriterijumi za uključivanje ispitanica u istraživanje bili su da su imale jedan prethodni terminski porođaj pre 6–18 meseci. Korišćena je anketa kreirana u elektronskom obliku upotrebom aplikacije *Google forms*. **Rezultati.** Seksualnu disfunkciju je prijavilo 21/69 (30%) ispitanica, a urinarnu inkontinenciju 8/69 (12%). Urinarna inkontinencija je bila značajno češća među ispitanicama sa rascepom porođajnog kanala ($p < 0,01$). Negativne emocionalne reakcije tokom seksualnog odnosa bile su učestalije kod ispitanica kod kojih je prošlo više vremena od porođaja ($p < 0,001$). Samo 3/21 (14%) ispitanica sa seksualnom disfunkcijom i 3/8 (38%) sa urinarnom inkontinencijom su prijavile problem svom lekaru. Lekar je pitao o problemu urinarne inkontinencije tokom redovne posete kod 16/69 (23%), a o seksualnoj disfunkciji kod 15/69 (22%) ispitanica. **Zaključak.** Seksualna disfunkcija i urinarna inkontinencija su česta stanja posle prvog porođaja. Trauma medice tokom porođaja može uzrokovati urinarnu inkontinenciju posle porođaja. Negativne emotivne reakcije tokom seksualnog odnosa se povećavaju tokom vremena koje protekne od porođaja. Pacijenti i lekari retko razgovaraju o seksualnoj disfunkciji i urinarnoj inkontinenciji. **Ključne reči:** urinarna inkontinencija; fiziološka seksualna disfunkcija; porođaj; akušerski porođaj; komplikacije akušerskog porođaja; postporođajni period; poremećaji karličnog dna; psihološki stres; emocije

function. Damage to these structures leads to pelvic floor dysfunction, which includes various conditions such as urinary incontinence, pelvic organ prolapse, and sexual dysfunction [1,2].

Urinary incontinence (UI) is a highly prevalent pelvic floor disorder, defined as a “complaint of involuntary loss

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Abbreviations

- UI – urinary incontinence
- SD – sexual dysfunction
- CIS – Clinical Information System
- PISQ-12 – Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire
- ICIQ-UI SF – International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form
- UCCV – University Clinical Center of Vojvodina

of urine” [3,4]. It commonly affects women and can impact multiple aspects of life, including social, psychological, occupational, and sexual domains. UI is associated with feelings of shame and a significant reduction in quality of life [5–7]. Risk factors may include pregnancy, mode of delivery, obesity, and maternal age [8]. The prevalence of urinary incontinence following childbirth is approximately 31% among primiparous women [9]. Management strategies range from conservative approaches, such as lifestyle modifications, pelvic floor muscle training, and biofeedback, to surgical interventions [10,11].

Women’s sexual health is a vital aspect of life at any age and is influenced by multiple factors. In particular, pregnancy and childbirth bring about biological, psychological, and social changes that may impact sexual health. Evidence suggests that sexual function declines during pregnancy and may not return to baseline levels during the postpartum period [12]. The American Psychiatric Association defines female sexual dysfunction (SD) as a condition that prevents an individual from experiencing satisfaction during sexual activity [13]. It has been reported that the rate of sexual dysfunction can reach up to 64% six months postpartum, and approximately 6.4% of women did not experience physical satisfaction in their sexual relationships 18 months after childbirth. Between 80% and 93% of women resume sexual activity within the first three months postpartum. During this period, two-thirds of women experience some form of sexual dysfunction, such as vaginal dryness, pain, reduced libido, or inability to achieve orgasm [14]. An important factor that may influence sexual dysfunction is the mode of delivery, which can be categorised as spontaneous vaginal delivery, episiotomy, assisted vaginal delivery, or caesarean section [15]. Management of sexual problems in women is typically individualised and multidisciplinary [16].

Material and Methods

The cross sectional study was conducted as a cross-sectional study at the Clinic of Gynaecology

and Obstetrics, University Clinical Center of Vojvodina (UCCV) in Novi Sad. A total of 69 women participated in the study. Inclusion criteria were primiparous women, 6 to 18 months postpartum, with a term pregnancy. Data were collected from the Clinical Information System (CIS) and via a questionnaire. The questionnaire was designed electronically using Google Forms. Participants were recruited by telephone, and the questionnaire was sent to them online via a link.

The questionnaire was developed for this study and included both customised questions designed by the authors and questions from the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12) and the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF). The questionnaire contained 31 questions, all of which were closed-ended except for one open-ended question. The questionnaire is available via the following link: <https://forms.office.com/Pages/ResponsePage.aspx?id=DQSIkWdsW0yxEjajBLZtrQAAAAAAAAAAAAAAAAAANAARtZWPUQTdOWE-JYWDQyRVhWTlc1TEI3OVlKM1lEMy4u>

Data were statistically analysed using IBM SPSS v27.0, with measures of central tendency and variability determined. The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Chi-square test, Fisher’s exact test, Student’s t-test, one-way ANOVA, Mann–Whitney U test, and Kruskal–Wallis test were applied to determine statistical significance at a level of $p < 0.05$.

The study was approved by the Ethics Committee of the UCCV under approval number 00-471.

This research was conducted as part of the project “Development of portable device for continence preservation”, financed by the Science Fund of the Republic of Serbia, PRISMA, Grant No. 7295.

Results

Of the total number of participants, 38/69 (55%) delivered vaginally, while 31/69 (45%) underwent caesarean section. Among the women who had a caesarean delivery, 18/31 (58%) were elective, and 13/31 (42%) were emergency caesarean sections.

Among women who delivered vaginally, an episiotomy was performed in 31/38 (82%), whereas 19/38 (50%) experienced obstetric soft tissue lacerations (cervical and/or perineal tears). In 2/38 (5.3%), the birth canal was intact. During vaginal delivery, fundal pres-

Table 1. Presence of specific factors during vaginal delivery

	Episiotomy N (%)	Kristeller maneuvr N (%)	Soft tissue lacerations N (%)
Yes	31 (82)	15 (39)	19 (50)
No	7 (18)	23 (61)	19 (50)

Table 2. Frequency of various delivery-related factors among patients with urinary incontinence and sexual dysfunction

	Mode of delivery		Laceration		Episiotomy		Kristeller maneuver	
	Vaginal	Caesarean section	Yes	No	Yes	No	Yes	No
Urinary incontinence	18.4%	3.2%	32%	10.5%	16%	43%	13%	26%
	p = 0.066		p = 0.004		p = 0.457		p = 1.000	
Sexual dysfunction	32%	29%	37%	47%	29%	43%	33%	30%
	p = 0.606		p = 0.151		p = 0.755		p = 1.000	

sure (Kristeller manoeuvre) was applied in 15/38 participants (39%) (Table 1).

Of the total number of participants, 66/69 (96%) reported resuming sexual activity postpartum. The mean time from delivery to the first sexual intercourse in our sample was 2.3 ± 1.1 months.

Among the participants who resumed sexual activity, 45/66 (68%) did not report any form of sexual dysfunction.

The remaining 21/66 (32%) reported sexual dysfunction, specifically: all 21/21 (100%) experienced pain in the genital area during or immediately after sexual activity, and 6/21 (29%) additionally reported negative emotional responses such as fear, disgust, shame, or guilt during sexual activity.

Uncontrolled urinary leakage postpartum was reported by 8/69 (12%) participants, of whom 7/8 (87.5%) had delivered vaginally.

In 6/8 (75%) participants, urinary incontinence occurred during sneezing or coughing, in 1/8 (12%) it occurred before reaching the toilet, and in 1/8 (12%) it occurred without a specific trigger (Figure 1).

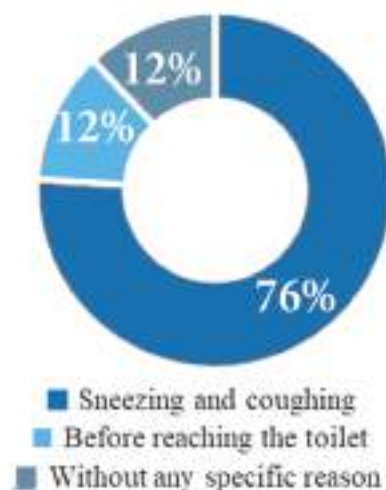
During routine postpartum check-ups, 16/69 (23%) participants were asked about urinary incontinence, and 15/69 (22%) were asked about sexual dysfunction.

Only 3/21 (14%) of women with sexual dysfunction spontaneously reported the problem to their physician, and 3/8 (38%) of women with urinary incontinence did so.

Postpartum pelvic floor rehabilitation in the form of Kegel exercises was performed by 7/69 (10%) participants, of whom 2/7 (29%) had urinary incontinence and 1/7 (14%) had sexual dysfunction (pain in the genital area).

Table 2 shows the influence of various delivery-related factors on the prevalence of urinary incontinence (UI) and sexual dysfunction (SD), as assessed using Fisher's exact test.

According to the Kruskal-Wallis test, there was a statistically significant difference ($p < 0.001$) in the mean time from delivery to the resumption of sexual activity in relation to the occurrence of negative emotional responses during sexual intercourse. Negative emotional responses during sexual activity increased with the time elapsed since delivery.

**Figure 1.** Prevalence of different situations in which involuntary urination occurred

Discussion

Although pregnancy and childbirth are physiological processes, they may be associated with potential physical complications. It is well established that up to 42% of postpartum women experience urinary incontinence (UI). Another important issue during and after pregnancy is changes in sexual life [17].

A 2022 study reported that the rate of episiotomy during spontaneous vaginal delivery in countries of the former Yugoslavia ranged from 30.9% in Slovenia to 62.8% in Serbia [18]. In our sample, the episiotomy rate among vaginal deliveries in primiparas was 82%.

According to a study by Farrington et al., which included 76 studies from 22 countries, the prevalence of the Kristeller manoeuvre ranged from 0.6% to 69.2% across studies, with a pooled prevalence of 23.2% [19]. In our study, the prevalence was 39%.

Perineal injury is a common event during childbirth, occurring in 30–80% of women [20]. Intrapartum cervical laceration is an obstetric complication that may occur in all modes of delivery. Clinically significant cervical lacerations are rare and complicate 0.1–5% of deliveries [21]. In our study, perineal and cervical injuries were classified as “obstetric soft tissue lacerations”, which were present in 50% of women who delivered vaginally.

Current research indicates that the prevalence of resumption of sexual activity after childbirth ranges from 30% to 60% within the first three months postpartum, decreasing to 17–31% six months after delivery [22]. In our study, 96% of participants reported resuming sexual activity after childbirth, with a mean time to resumption of 2.3 months postpartum.

Nearly two-thirds of women (64.3%) have reported experiencing sexual dysfunction during the first year postpartum. The most commonly reported types of sexual dysfunction include disorders of sexual desire (81.2%) [23]. In our study, 21/66 (32%) participants reported sexual dysfunction in the form of pain in the genital area during and immediately after sexual intercourse, with 6 participants additionally reporting negative emotional responses. However, this result might be influenced by the relatively small sample.

The prevalence of urinary incontinence in the postpartum period ranges from 3% to 40% [24]. Stress urinary incontinence is characterised by sudden involuntary leakage of urine during activities that increase intra-abdominal pressure [25]. In our study, 12% of participants experienced urinary incontinence, which occurred during sneezing and coughing in 75% of cases.

Patient-related barriers to discussing sexual function include fear of embarrassment or concern that their problems may be dismissed. In addition, healthcare providers rarely ask about or initiate discussions regarding sexual function. Clinician-related barriers to discussing sexual function include feelings of embarrassment, lack of communication skills, and insufficient knowledge and training regarding available treatment options [26]. In our study, 23% of participants were asked about urinary incontinence during medical visits, while 22% were asked about sexual dysfunction. Of the participants who experienced urinary incontinence, 38% reported the problem to their physician, whereas only 14% of those with sexual dysfunction did so.

Kegel exercises are a therapeutic intervention aimed at improving pelvic floor muscle function. Current evidence suggests that this therapy is suitable for routine postpartum exercise and has beneficial effects in improving urinary incontinence, vaginitis, and puerperal symptoms [27,28]. In our study, 10% of participants performed Kegel exercises after childbirth.

Numerous epidemiological studies have supported a causal relationship between vaginal delivery and urinary incontinence [29]. A study by McArthur et al. demonstrated that caesarean section does protect against subsequent urinary incontinence, with 40% of women reporting urinary incontinence even after caesarean delivery [30]. In our study, we found no statistically significant association between mode of delivery and the occurrence of urinary incontinence (7/38 [18.4%] vagi-

nal delivery vs 1/31 [3.2%] caesarean section); however this result might be influenced by the relatively small sample. Cattani et al. reported that caesarean section, compared with vaginal delivery, reduces the risk of dyspareunia but not sexual dysfunction [31]. Similarly, in our study, no statistically significant association was observed between mode of delivery and sexual dysfunction or urinary incontinence.

In a study by Gommesen et al., the proportion of women reporting urinary incontinence after perineal tears ranged from 15% to 25% among women with third- or fourth-degree tears, and from 5% to 15% among women with first- or second-degree tears [32]. Another study by Gommesen et al. showed that more than half of women who sustained anal sphincter rupture also experienced dyspareunia [33]. In our study, a statistically significant association was found between obstetric soft tissue lacerations and urinary incontinence, but no association was observed with sexual dysfunction.

No significant associations were found between episiotomy and urinary incontinence, consistent with the majority of studies examining different types of episiotomy [34]. These findings are consistent with our results, which showed no statistically significant association between episiotomy and urinary incontinence. According to a study from Vietnam, 40.7% of women who underwent episiotomy reported symptoms of sexual dysfunction postpartum [35]. In our study, no statistically significant association was found between episiotomy and sexual dysfunction.

Sartore et al. showed that dyspareunia was significantly more frequent among women who underwent Kristeller manoeuvre, whereas urinary incontinence did not differ significantly between groups [36]. In our study, no statistically significant association was found between the Kristeller manoeuvre and urinary incontinence or sexual dysfunction.

The absence of a statistically significant association between episiotomy and the Kristeller manoeuvre and the occurrence of SD and UI suggests that these interventions were not associated with an increased risk of pelvic floor dysfunction; however, this finding alone does not provide evidence of a protective effect.

Among postpartum women in the United States and Australia, approximately 26–41% resumed sexual activity within six weeks after childbirth, with the majority resuming within the first 12 weeks. Women may require time to feel both physically and emotionally comfortable before resuming sexual activity after childbirth [37]. In our study, no statistically significant difference was observed in the mean time from delivery to resumption of sexual activity in relation to the presence of genital pain during or after sexual inter-

course; however, negative emotional responses during sexual activity were found to increase with the time elapsed since delivery.

Addressing these issues requires efforts from healthcare providers, patients, and society as a whole. Greater education regarding the management of these patients, increased research engagement, and improved knowledge of available treatment options are needed. Efforts should also be directed towards reducing stigma surrounding urinary incontinence and sexual dysfunction among women and within society to promote more open communication between physicians and patients and to reduce feelings of shame and embarrassment on both sides.

Conclusion

The conclusions drawn from the results should be interpreted with caution owing to the small sample size

- Sexual dysfunction and urinary incontinence are common conditions associated with childbirth
- Perineal trauma during childbirth may contribute to the development of postpartum urinary incontinence.
- Negative emotional responses during sexual intercourse increase with the time elapsed since childbirth.
- Discussions about sexual dysfunction and urinary incontinence between patients and healthcare providers are infrequent and should be encouraged.

References

1. Peinado-Molina RA, Hernández-Martínez A, Martínez-Vázquez S, Rodríguez-Almagro J, Martínez-Galiano JM. Pelvic floor dysfunction: prevalence and associated factors. *BMC Public Health*. 2023;23(1):2005.
2. Zhu H, Zhang D, Gao L, Liu H, Di Y, Xie B, et al. Effect of pelvic floor workout on pelvic floor muscle function recovery of postpartum women: protocol for a randomized controlled trial. *Int J Environ Res Public Health*. 2022;19(17):11073.
3. Russo E, Caretto M, Giannini A, Bitzer J, Cano A, Ceausu I, et al. Management of urinary incontinence in postmenopausal women: an EMAS clinical guide. *Maturitas*. 2021;143:223-30.
4. Ruffolo AF, Lallemand M, Garabedian C, Deseure A, Kergage Y, Rubod C, et al. The impact of pregnancy and childbirth on stress urinary incontinence in women previously submitted to mid-urethral sling: a systematic review and meta-analysis. *Neurourology Urology*. 2024;43(7):1631-46.
5. Von Aarburg N, Veit-Rubin N, Boulvain M, Bertuit J, Simonson C, Desseauve D. Physical activity and urinary incontinence during pregnancy and postpartum: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2021;267:262-8.
6. Dominguez-Antuña E, Diz JC, Suárez-Iglesias D, Ayán C. Prevalence of urinary incontinence in female CrossFit athletes: a systematic review with meta-analysis. *Int Urogynecol J*. 2023;34(3):621-34.
7. Sazonova NA, Kiseleva MG, Gadzhieva ZK, Gvozdev MY. Urinary incontinence in women and its impact on quality of life. *Urologia*. 2022;(2):136-9.
8. Hage-Fransen MAH, Wiezer M, Otto A, Wieffer-Platvoet MS, Slotman MH, Nijhuis-van der Sanden MWG, et al. Pregnancy- and obstetric-related risk factors for urinary incontinence, fecal incontinence, or pelvic organ prolapse later in life: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2021;100(3):373-82.
9. Zhang D, Bo K, Montejó R, Sánchez-Polán M, Silva-José C, Palacio M, et al. Influence of pelvic floor muscle training alone or as part of a general physical activity program during pregnancy on urinary incontinence, episiotomy and third- or fourth-degree perineal tear: systematic review and meta-analysis of randomized clinical trials. *Acta Obstet Gynecol Scand*. 2024;103(6):1015-27.
10. Yang X, Zhang A, Sayer L, Bassett S, Woodward S. The effectiveness of group-based pelvic floor muscle training in preventing and treating urinary incontinence for antenatal and postnatal women: a systematic review. *Int Urogynecol J*. 2022;33(6):1407-20.
11. Mladenović-Segedi L. Improvement in the quality of life in women with stress urinary incontinence after surgery for pelvic organ prolapse. *Med Pregl*. 2019;72(7-8):197-201.
12. Gutzeit O, Levy G, Lowenstein L. Postpartum female sexual function: risk factors for postpartum sexual dysfunction. *Sex Med*. 2020;8(1):8-13.
13. Ng YY, Muhamad R, Ahmad I. Sexual dysfunction among six months postpartum women in north-eastern Malaysia. *PLoS One*. 2023;18(4):e0284014.
14. Hosseini L, Iran-Pour E, Safarinejad MR. Sexual function of primiparous women after elective cesarean section and normal vaginal delivery. *Urol J*. 2012;9(2):498-504.
15. Fanshawe AM, De Jonge A, Ginter N, Takács L, Dahlen HG, Swertz MA, et al. The impact of mode of birth, and episiotomy, on postpartum sexual function in the medium- and longer-term: an integrative systematic review. *Int J Environ Res Public Health*. 2023;20(7):5252.
16. Kingsberg SA, Knudson G. Female sexual disorders: assessment, diagnosis, and treatment. *CNS Spectr*. 2011;16(2):49-62.
17. Schütze S, Heinloth M, Uhde M, Schütze J, Hüner B, Janni W, et al. The effect of pelvic floor muscle training on pelvic floor function and sexuality postpartum. A randomized study including 300 primiparous. *Arch Gynecol Obstet*. 2022;306(3):785-93.
18. Drandić D, Drglin Z, Mihevc Ponikvar B, Bohinec A, Čerimagić A, Radetić J, et al. Women's perspectives on the quality of hospital maternal and newborn care around the time of childbirth during the COVID-19 pandemic: results from the IMAGiNE EURO study in Slovenia, Croatia, Serbia, and Bosnia-Herzegovina. *Int J Gynaecol Obstet*. 2022;159(Suppl 1):54-69.
19. Farrington E, Connolly M, Phung L, Wilson AN, Comrie-Thomson L, Bohren MA, et al. The prevalence of uterine fundal pressure during the second stage of labour for women giving birth in health facilities: a systematic review and meta-analysis. *Reprod Health*. 2021;18(1):98.
20. Venugopal V, Deenadayalan B, Maheshkumar K, Yogapriya C, Akila A, Pandiaraja M, et al. Perineal massage for prevention of perineal trauma and episiotomy during labor: a systematic review and meta-analysis. *J Family Reprod Health*. 2022;16(3):162-9.
21. Hossein-Pour P, Rajasingham M, Muraca GM. Risk of cervical laceration in forceps vs vacuum delivery: a systematic

review and meta-analysis. *Acta Obstet Gynecol Scand.* 2025;104(1):29-38.

22. Zhang Q, Shen M, Zheng Y, Jiao S, Gao S, Wang X, et al. Sexual function in Chinese women from pregnancy to postpartum: a multicenter longitudinal prospective study. *BMC Pregnancy Childbirth.* 2021;21(1):65.

23. Khajehei M, Doherty M, Tilley PJ, Sauer K. Prevalence and risk factors of sexual dysfunction in postpartum Australian women. *J Sex Med.* 2015;12(6):1415-26.

24. Höder A, Stenbeck J, Fernando M, Lange E. Pelvic floor muscle training with biofeedback or feedback from a physiotherapist for urinary and anal incontinence after childbirth - a systematic review. *BMC Womens Health.* 2023;23(1):618.

25. Lugo T, Leslie SW, Mikes BA, Riggs J. Stress urinary incontinence. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2026 [cited 2026 Jun 25]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539769/>

26. Merriam S, Kling JM, Thomas HN, Casas RS. Female sexual dysfunction: a primer for primary care health professionals. *MedEdPORTAL.* 2023;19:11312.

27. Chen H, Yang N, Yang H, Huang G, Zhou W, Ying Q, et al. Efficacy of Kegel exercises combined with electrical stimulation on the restoration of postpartum pelvic floor muscle function. *Am J Transl Res.* 2023;15(1):622-9.

28. Yount SM, Fay RA, Kissler KJ. Prenatal and postpartum experience, knowledge and engagement with Kegels: a longitudinal, prospective, multisite study. *J Womens Health.* 2021;30(6):891-901.

29. Ren Y, Hu Q, Zou H, Xue M, Tian X, Cao F, et al. Age at first birth and risk of urinary incontinence after delivery: a dose-response meta-analysis. *Sci Rep.* 2022;12(1):16588.

Rad je primljen 31. V 2026.

Recenziran 4. VIII 2026.

Prihvaćen za štampu 9. VIII 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:182-187.

30. MacArthur C, Glazener C, Lancashire R, Herbison P, Wilson D. Exclusive caesarean section delivery and subsequent urinary and faecal incontinence: a 12-year longitudinal study. *BJOG.* 2011;118(8):1001-7.

31. Cattani L, De Maeyer L, Verbakel JY, Bosteels J, Deprest J. Predictors for sexual dysfunction in the first year postpartum: a systematic review and meta-analysis. *BJOG.* 2022;129(7):1017-28.

32. Gommesen D, Hjorth S, Nøhr EA, Qvist N, Rasch V. Obstetric perineal tears, birth characteristics and the association with urinary incontinence among primiparous women 12 months postpartum: a prospective cohort study. *Int Urogynecol J.* 2024;35(10):2033-44.

33. Gommesen D, Nøhr E, Qvist N, Rasch V. Obstetric perineal tears, sexual function and dyspareunia among primiparous women 12 months postpartum: a prospective cohort study. *BMJ Open.* 2019;9(12):e032368.

34. Živković K, Orešković S, Cerovac A, Milošević M, Luetić AT, Prka M, et al. Effects of lateral episiotomy on the emergence of urinary incontinence during the first postpartum year in primiparas: prospective cohort study. *Prz Menopauzalny.* 2021;20(4):163-9.

35. Quoc Huy NV, Phuc An LS, Phuong LS, Tam LM. Pelvic floor and sexual dysfunction after vaginal birth with episiotomy in Vietnamese women. *Sex Med.* 2019;7(4):514-21.

36. Sartore A, De Seta F, Maso G, Ricci G, Alberico S, Borelli M, et al. The effects of uterine fundal pressure (Kristeller maneuver) on pelvic floor function after vaginal delivery. *Arch Gynecol Obstet.* 2012;286(5):1135-9.

37. Gillen MM, Rosenbaum DL, Markey CH. Body image and sex among postpartum women. *Body Image.* 2025;52:101852.

REVIEW ARTICLES PREGLEDNI ČLANCI

THE ROLE OF GLP-1 AGONISTS IN THE TREATMENT OF INFLAMMATORY DERMATOSES

ULOGA GLP-1 AGONISTA U TERAPIJI INFLAMATORNIH DERMATOZA

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Review article

Pregledni članak

UDK 616.5-002-085.35

<https://doi.org/10.2298/MPNS2608189S>

Abstract

Introduction. According to the latest studies, glucagon-like peptide-1 receptor agonists, in addition to reducing glycaemia and body weight, also exert strong anti-inflammatory and immunomodulatory effects and are increasingly used to treat chronic inflammatory dermatoses. **Glucagon-like peptide-1 receptor agonists and psoriasis vulgaris.** In practice, positive effects of glucagon-like peptide-1 receptor agonists on psoriasis severity associated with insulin resistance/diabetes mellitus type 2 and obesity have been observed. In various studies, glucagon-like peptide-1 receptor agonists resulted in significant reductions in psoriasis severity scores and improvements in quality of life. Studies have shown significant improvements in clinical picture and quality of life with **glucagon-like peptide-1 receptor agonists** in patients with **hidradenitis suppurativa** associated with obesity. **Discussion.** Psoriasis and hidradenitis suppurativa are dermatoses characterised by complex immune-mediated inflammatory processes. Clinical studies indicate that the use of glucagon-like peptide-1 receptor agonists leads to improvement of the clinical picture and skin changes in these patients who are obese and have type 2 diabetes/metabolic syndrome. **Conclusion.** Due to their metabolic, anti-inflammatory, and immunomodulatory effects, glucagon-like peptide-1 receptor agonists represent a promising therapeutic option for inflammatory dermatoses. Their effects are attributable not solely to weight loss but also to direct immunomodulatory action, which explains their efficacy independent of body weight reduction. Further randomised, placebo-controlled clinical trials are required to confirm their effectiveness.

Key words: Glucagon-Like Peptide-1 Receptor Agonists; Immunomodulating Agents; Psoriasis; Hidradenitis Suppurativa; Skin Diseases; Inflammation; Therapeutics; Diabetes Mellitus, Type 2; Treatment Outcome

Sažetak

Uvod. Agonisti receptora glukagonu sličnog peptida-1 utiču na snižavanje nivoa glikemije i smanjenje telesne mase te se koriste u lečenju dijabetesa melitusa tip 2 i gojaznosti. Prema nedavnim studijama, ovi lekovi imaju i antiinflamatorno i imunomodulatorno dejstvo, te sve više nalaze primenu u lečenju hroničnih inflamatornih dermatoza. **Agonisti receptora glukagonu sličnog peptida-1 i psoriasis vulgaris.** U praksi su uočeni pozitivni efekti agonista receptora glukagonu sličnog peptida-1 na težinu kliničke slike psorijaze udružene sa insulinskom rezistencijom/dijabetesom melitus tip 2 i gojaznošću. U različitim studijama upotrebom agonista receptora glukagonu sličnog peptida-1 došlo je do značajnog smanjenja skora zahvaćene površine i težine psorijaze i poboljšanja skora kvaliteta života. **Agonisti receptora glukagonu sličnog peptida-1 i hidradenitis suppurativa.** Studije su pokazale značajno poboljšanje kliničke slike i kvaliteta života kod upotrebe agonista receptora glukagonu sličnog peptida-1 kod pacijenata kod kojih je hidradenitis suppurativa udružen sa gojaznošću. **Diskusija.** U osnovi nastanka psorijaze i supurativnog hidradenitisa je veoma složen imunoposredovan inflamatorni proces. Kliničke studije i prikazi slučajeva ukazuju da upotreba agonista receptora glukagonu sličnog peptida-1 dovodi do poboljšanja kliničke slike i kožnih promena kod ovih pacijenata, a koji su gojazni i imaju dijabetes tip 2/ metabolički sindrom. **Zaključak.** Zahvaljujući ne samo metaboličkom, već i antiinflamatornom i imunomodulatornom dejstvu, agonisti receptora glukagonu sličnog peptida-1 predstavljaju obećavajuću terapijsku opciju u lečenju inflamatornih dermatoza. Njihov povoljan efekat nije posledica samo gubitka telesne mase, već i direktnog imunomodulatornog dejstva, što objašnjava njihovu efikasnost nezavisno od redukcije telesne mase. Potrebna su dalja randomizovana, placebo kontrolisana klinička ispitivanja kako bi se potvrdila njihova efikasnost.

Cljučne reči: agonisti receptora GLP-1; imunomodulatorni agensi; psorijaza; hidradenitis suppurativa; bolesti kože; inflamacija; terapija; dijabetes melitus tip 2; ishod lečenja

Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that regulates blood glucose levels by stim-

ulating insulin secretion and inhibiting glucagon secretion [1,2]. In addition, GLP-1 has physiological effects, including reducing nutrient absorption, delaying gastric emptying, suppressing appetite, improving

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Abbreviations

DPP-4	- dipeptidyl peptidase-4
NK cells	- natural killer cells
STAT1	- signal transducer and activator of transcription 1
NF- κ B	- nuclear factor κ B
T2DM	- type 2 diabetes mellitus
IL	- interleukin
iNKT	- invariant Natural Killer T-cells
PASI score	- Psoriasis Area and Severity Index score
DLQI score	- dermatology life quality index score
BMI	- body mass index
VAS	- visual analogue scale
CRP	- C-reactive protein
HS	- hidradenitis suppurativa
HS-PGA	- HS-Physician's Global Assessment
HSS	- Hurley Staging System
GLP-1	- glucagon-like peptide-1
GLP-1R	- glucagon-like peptide-1 receptor
TNF α	- tumour necrosis factor α
IFN- γ	- interferon- γ
GLP-1RA	- glucagon-like peptide-1 receptor agonists

lipid metabolism, inhibiting apoptosis, and inducing pancreatic β -cell neogenesis [2]. GLP-1 is produced predominantly by intestinal endocrine epithelial cells (L-cells) following food intake and then binds to glucagon-like peptide-1 receptors (GLP-1R). These receptors are present in various cells and tissues, primarily in the endocrine pancreas, where their activation leads to insulin secretion [2,3].

However, GLP-1 receptors are also found in other cells and tissues such as keratinocytes, endothelial cells, neurons, astrocytes, intraepithelial lymphocytes, neutrophils and eosinophils. Also, GLP-1R is expressed in the kidneys, lungs, heart, and hypothalamus, which suggests that GLP-1 may have additional roles in the body unrelated to glycaemia regulation [1,2,4,5].

GLP-1 also slows gastrointestinal motility, leading to delayed gastric emptying and a prolonged feeling of satiety [6]. It also acts through its receptors in the satiety and hunger centres in the hypothalamus, reducing food intake and making GLP-1 an important factor in weight control and obesity treatment [7].

GLP-1 also has cardioprotective, neurotropic and anti-inflammatory effects [8].

Impaired GLP-1 secretion, either reduced or excessively high, can lead to metabolic disorders, including obesity and reactive postprandial hypoglycaemia. Research shows that GLP-1 also has significant effects on cardiovascular function, including modulation of heart rate and blood pressure, further highlighting its therapeutic potential beyond glycaemic control [6].

Although GLP-1R expression in the skin has been confirmed, its role has not yet been fully elucidated [1,9]. Receptors for the GLP-1 hormone have also been found in immune cells that can infiltrate the skin. A study by Faurschou et al. examined the presence of GLP-1R in keratinocytes, immune cells and skin bi-

opsy samples from healthy volunteers and patients with psoriasis. GLP-1Rs were found in five of six skin biopsies from psoriatic plaques, one of six biopsies from non-psoriatic skin, and one of six healthy skin biopsies. When cultured keratinocytes were stimulated with tumour necrosis factor α (TNF- α) and interferon γ (IFN- γ), no GLP-1R expression was detected. This suggests that the presence of GLP-1R in biopsies from patients with psoriasis is likely due to infiltration of diseased skin by immune cells [10].

GLP-1 analogues are drugs that act as glucagon-like peptide-1 receptor agonists (GLP-1RA). They are synthetic polypeptides that are more resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) compared with natural GLP-1 and are also eliminated from the body more slowly. GLP-1R agonists lower glycaemia in hyperglycaemic states, reduce glucagon secretion in both hyperglycaemic and euglycaemic states, and slow gastric emptying [1,2,4]. In addition, GLP-1R agonists contribute to weight loss by acting on appetite centres in the hypothalamus [11]. In addition to their metabolic effects, GLP-1R agonists show cardioprotective effects, reducing the risk of cardiovascular events such as stroke and myocardial infarction [11]. Owing to all these effects, GLP-1R agonists are now used to treat patients with inflammation-dependent diabetic complications, such as diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease [2,12].

GLP-1Rs are present in distinct subpopulations of immune cells, allowing GLP-1R agonists to exert significant immunomodulatory effects [4].

Research has shown that GLP-1R agonists can prevent the recruitment of various types of immune cells (T-lymphocytes, NK (natural killer) cells, B-lymphocytes, leukocytes and dendritic cells) in inflamed tissue and reduce tissue infiltration by immune cells, which is one of the main mechanisms for weakening the inflammatory response [2].

In 2012, Lee and colleagues reported that GLP-1 reduced macrophage infiltration in adipocytes of obese mice. Likewise, GLP-1 exerts anti-inflammatory effects by reducing the expression of chemotactic factors, such as STAT1 (Signal transducer and activator of transcription 1), induced by IFN- γ , which are necessary for T-cell recruitment [13].

New research shows that GLP-1 can modulate the activities of NF- κ B (Nuclear factor- κ B). It is a family of protein complexes that act as primary mediators of pro-inflammatory gene induction and are activated in response to cellular stress, pathogens, and cytokines. Studies show that GLP-1 reduces NF- κ B activity in inflamed tissues by reducing TNF- α synthesis. TNF- α plays a key role in the pathogenesis of inflammatory diseases, including hidradenitis sup-

purativa (HS), by promoting the expression of NF- κ B, thereby exacerbating inflammation [13,14].

In their research, the authors showed that *sitagliptin* exerts its anti-inflammatory effects by inhibiting NF- κ B, indicating that inhibition of NF- κ B signalling pathways is another potential mechanism by which GLP-1 exerts anti-inflammatory effects in both diabetic and non-diabetic settings [15].

There is strong evidence that GLP-1RAs reduce the inflammatory response by lowering oxidative stress and normalising the redox state in experimental rats and diabetic patients [16].

GLP-1R agonists are a new class of antidiabetic drugs; in addition to their hypoglycaemic effects, they can also have anti-inflammatory effects. They can prevent inflammatory events through at least five molecular mechanisms: improving glucose homeostasis and reducing glucotoxicity, normalising the redox state and reducing inflammation caused by oxidative stress, suppressing the recruitment of leukocytes to inflamed tissue, reducing lipotoxicity and downregulating various inflammatory mediators [13,16].

Because of all this, GLP-1R analogues have found wider application in clinical practice, not only for the treatment of patients with type 2 diabetes mellitus (T2DM) and its complications, but also in dermatology for inflammatory dermatoses [13,16].

GLP-1 agonists and psoriasis vulgaris

Psoriasis vulgaris is a chronic inflammatory dermatosis, affecting approximately 0.27 to 11.4% of the world's population, depending on the geographical area. Chronic inflammation of the skin is at the root of the disease, but systemic inflammation is also present in these patients. Up to 10-40% of patients with psoriasis also develop psoriatic arthritis [17]. Also, patients with psoriasis have a higher risk of adverse cardiovascular events, such as heart attack and stroke, and more often have comorbidities such as obesity, type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, and inflammatory bowel disease [18-20]. Frequent stigmatisation contributes to a significantly lower quality of life and to a higher incidence of psychiatric disorders such as depression and anxiety, abuse of alcohol or psychoactive substances [17,21].

Psoriasis is a chronic immune-mediated skin disease characterised by dysregulation of the immune system in terms of increased activation of immune cells, especially T-lymphocytes, together with other key inflammatory cells, such as macrophages and dendritic cells, which leads to the initiation of a cascade of inflammatory reactions that significantly contribute to the development and duration of the disease [22].

During this process, activated T cells and inflammatory cells release inflammatory mediators such as TNF- α and IFN- γ . Activation of interleukin (IL)-23 and Th17 cells leads to abnormal keratinocyte proliferation and further release of pro-inflammatory cytokines, forming a positive feedback loop. In addition, keratinocytes secrete antimicrobial peptides, cytokines, and chemokines that promote immune cell infiltration [1,22]. Previous research has shown that IL-17 plays a key role in the pathogenesis of psoriasis by triggering the secretion of three different classes of cytokines [23].

Research has shown that GLP-1R agonists reduce the activity of Invariant Natural Killer T-cells (iNKT), resulting in decreased secretion of proinflammatory cytokines such as IFN- γ , IL-2, IL-4, IL-17, and TNF- α . Also, it is believed that GLP-1R agonists can increase the production of anti-inflammatory cytokines, such as IL-10, and simultaneously reduce IL-17 production by attenuating the activation of dermal $\gamma\delta$ T-cells. GLP-1R agonists also reduce lymphocyte migration, inhibit signalling pathways involved in immune cell proliferation and migration, and reduce transcription of pro-inflammatory cytokines [24].

Considering the very complex immune-mediated inflammatory process underlying psoriasis, positive effects of GLP-1R agonists (*semaglutide*, *liraglutide*, *exenatide*) on the severity of the clinical picture of psoriasis associated with insulin resistance/T2DM and obesity have been observed in practice [1].

In these studies, the use of GLP-1R agonists resulted in a significant reduction in the affected area score and psoriasis severity index (PASI), and an improvement in the quality-of-life score (DLQI), over 3 months to 1 year [1,25].

In a 2012 case report, the introduction of *exenatide* into the therapy of a 61-year-old patient with psoriasis and T2DM resulted in a significant reduction in the PASI score (11 $\rightarrow$ 3) and improved glycaemic control over a period of one year [26].

Likewise, in a 73-year-old patient with psoriasis and T2DM, after 4 months of semaglutide use, there was a significant reduction in PASI (33.2 $\rightarrow$ 2.6) and DLQI (26 $\rightarrow$ 0) scores [27].

The use of semaglutide showed efficacy in another study conducted in 2023 in Italy, in an obese patient suffering from psoriasis and T2DM. After 4 months, there was a reduction in body weight, PASI and DLQI scores, as well as improved glycoregulation [28].

Also, two cases of liraglutide use in patients with diabetes and psoriasis have been reported in the literature. In one patient, a reduction in itching and desquamation was observed after a few days of liraglutide administration. After three months of administration, there was further improvement in both psoriasis and

glycaemic regulation, as well as weight loss [29]. Another patient who, in addition to psoriasis, was also obese, used acitretin for many years. One year after the introduction of liraglutide, there was a significant improvement in psoriasis and a reduction in body weight, accompanied by decreases in both PASI and DLQI scores [30].

Three prospective cohort studies and one case study analysed the use of liraglutide in the treatment of patients with psoriasis and T2DM. After liraglutide administration for 6 to 20 weeks, a significant reduction in PASI scores was observed in all four studies [26,31–33]. Three studies also showed significant improvements in quality of life among these patients and reductions in DLQI scores [26,31,32]. In these patients, there was also an improvement in lipid status parameters and HbA1c, and a decrease in body mass index (BMI) [26,31–33].

Randomised controlled studies have also been conducted on this topic. In a study conducted in China, 12 patients with psoriasis and T2DM received liraglutide, while a control group of 13 patients received acitretin, calcipotriol, and oral antidiabetics for 12 weeks. In the study group that received liraglutide, significant improvement in PASI and DLQI was observed, along with decreased expression of IL-23 and IL-17 in the skin of patients with psoriasis [34].

Another placebo-controlled study was conducted in Denmark. The test and control groups comprised 20 patients with psoriasis and preserved glucose tolerance, with one group receiving liraglutide and the other receiving placebo. This study showed no statistically significant differences in PASI and DLQI after 8 weeks of treatment with liraglutide (n=11) versus placebo (n=9) [35].

In addition to the positive effects on psoriatic skin changes with GLP-1R agonists, reductions in comorbidities were observed among the examined patients.

In the study by Nicolau et al., 20 obese patients with psoriasis were examined. They were treated with liraglutide 3 mg for 3 months. An average decrease in PASI score from 10 to 5.1 was recorded in almost 50% of subjects, as well as a significant decrease in body mass index, pain intensity on the Visual analogue scale (VAS), and levels of C-reactive protein (CRP), homocysteine, ferritin, and cortisol in plasma [36].

In a prospective cohort study of 7 patients with psoriasis and T2DM treated with *liraglutide* for 12 weeks, a mean reduction in PASI from 15.7 to 2.2 and an improvement in DLQI from 21.8 to 4.1 were observed. In addition, reductions in HbA1c, BMI and waist circumference were observed [33].

A 2025 study by Olbrich et al. involving more than 6,000 patients with psoriasis and diabetes or obesity

compared outcomes between patients who received GLP-1R agonists and those treated with other anti-diabetic or anti-obesity therapies. Psoriasis patients treated with GLP-1R agonists were found to have a 78% lower risk of death and a 44% lower risk of major cardiovascular events compared with those taking other drugs for diabetes or weight loss. Also, in these patients, treatment with GLP-1R agonists significantly reduced the risk of alcohol abuse by 65% and substance abuse by almost 50%. This risk reduction was more pronounced in patients with psoriasis compared with obese or diabetic subjects without psoriasis, suggesting a direct causal benefit of GLP-1R agonists [21].

Also, in the studies published so far, there is only one recorded case of worsening of the clinical picture of psoriasis after the use of the GLP-1R agonist - liraglutide. After the start of liraglutide administration, there was not only a worsening of psoriasis, but also the development of local resistance. After stopping liraglutide, the clinical picture of psoriasis improved. One possible explanation for the worsening of psoriasis is a cytokine imbalance, similar to the exacerbation of psoriatic changes in some people after biological therapy [37].

GLP-1 agonists and hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease affecting apocrine glands [38]. The prevalence of HS ranges from 0.5% to 1% of the general population [4]. It most often affects intertriginous areas where nodules, abscesses, cysts and sinuses are formed, which is accompanied by the persistent presence of purulent content and severe pain [4,38,39].

The aetiopathogenesis of HS is very complex and not fully understood. It is believed that genetic predisposition, environmental factors and immune system dysregulation play significant roles in the development of the disease [4]. In particular, obesity stands out as a risk factor, which represents both a predisposing and aggravating factor for HS [40]. In people with HS, obesity increases skin friction in the intertriginous areas, leading to increased expression of pro-inflammatory markers and an influx of neutrophils and macrophages. Increased immune cell activity induces oxidative stress and low-grade systemic inflammation, thereby promoting progression of HS lesions and increasing overall disease severity [40]. In addition, the micro-conditions within the skin folds of the obese, such as moisture, friction, maceration and an anaerobic environment, further contribute to the development of lesions [41].

A damaged skin barrier in obese people not only worsens existing lesions but also hinders their remission. Also, slower wound healing has been observed

in obese people and metabolic syndrome and T2DM are often present at the same time [42,43].

Numerous studies have shown that the prevalence of HS is significantly higher in obese people. As many as 18-20% of obese patients may suffer from HS, which is a significantly higher rate compared with the general population [44,45].

Studies have also shown that weight loss is positively associated with reduced severity and prevalence of HS symptoms [46].

Likewise, research has shown that patients with HS have a threefold higher risk of developing diabetes compared with the general population, and that is why screening for DM in these patients is important [40].

In patients with HS and BMI >30 kg/m², increased expression of the IL-17 receptor (an important pro-inflammatory cytokine implicated in the pathogenesis of HS) was observed and is considered a key rationale for the use of GLP-1R agonists in their treatment. In addition to the metabolic benefits of using GLP-1R agonists, this therapy can also lead to positive effects due to its anti-inflammatory and immunomodulatory effects, as well as in psoriasis [47].

Unlike psoriasis, where in most patients the effectiveness of biological drugs interleukin-23 and -17 inhibitors has made completely clear skin a realistically expected treatment goal, in patients with hidradenitis suppurativa there are still no drugs that can achieve a similar degree of clinical improvement. Given these significant unmet needs in hidradenitis suppurativa, all mechanisms and drugs that can improve clinical response are of great importance [48].

So far, less research has been published on the potential benefit of GLP-1R agonists in the treatment of HS than in psoriasis [1].

In a systematic review, Krajewski et al. reported that in patients with HS, GLP-1R agonists, particularly liraglutide and semaglutide, significantly reduced clinical severity and systemic inflammation. Improvements in lesion severity (reduction of inflammatory nodules, abscess formation and overall disease severity) and quality of life were observed [4].

The anti-inflammatory effects of GLP-1RAs are based on the inhibition of key inflammatory pathways involving TNF- α , IL-17 and NF- κ B that contribute to the pathogenesis of HS. Also, GLP-1R agonists reduce iNKT levels, which is significant because activation of these cells increases the expression of pro-inflammatory cytokines such as IFN- γ , TNF- α , and IL-17 [14,32,49].

These positive anti-inflammatory effects correlate with improvements in the clinical picture and symptoms in patients with HS. In their work published in 2017, Jennings et al. describe the case of an obese pa-

tient who was a smoker and had a severe form of HS (DLQI score 24 and HS-Physician's Global Assessment (HS-PGA) score 4), with a significantly impaired quality of life. The patient used narcotic analgesics daily for pain regulation. Since the patient was resistant to local and systemic HS therapy, liraglutide was introduced into the therapy. After 4 weeks of treatment, there was a significant improvement in the clinical picture, a decrease in the HS-PGA score to 1, and the patient used analgesics less often. GLP-1R agonists have been shown to reduce the secretion of IL-17 and TNF- α induced cytokines, both of which are important in the development of HS. It is considered that the improvement of the clinical picture of HS (reduction of both scores) is probably due to both the direct anti-inflammatory effect of liraglutide, through activation of the GLP-1 receptor, and the indirect effect of liraglutide, through body weight reduction [50].

A prospective case series conducted in 2024 in Spain included 14 patients with HS and obesity who were treated with liraglutide for 3 months. The results of the study showed a statistically significant decrease in body mass index and waist circumference, as well as a decrease in markers of inflammation (CRP, homocysteine, cortisol). The Hurley Staging System (HSS) was used to assess the severity of HS lesions, and the DLQI score was used to assess the quality of life. After therapy, both scores decreased, but the change was not statistically significant [36].

Other studies have also shown a connection between HS and obesity, that is, that weight loss can alleviate the severity of HS. A study by Gupta et al. examined the use of semaglutide, tirzepatide, dulaglutide, and liraglutide in 22 obese subjects with diabetes and HS. The drugs were primarily given to treat obesity or diabetes; however, 68.2% of subjects also noted an improvement in the clinical picture of HS. The respondents observed a decrease in inflammation (61.9%), a decrease in the appearance of new lesions (66.7%), a decrease in pain (52.4%), a decrease in the drainage of contents (61.9%), a decrease in itching (47.6%) and an unpleasant odour (42.9%). About 59.1% of respondents said they would recommend using GLP-1RA [51].

Also, Lyons et al. found in a study of 30 obese patients with HS that *semaglutide*, even at a low dose (0.8 mg per week), can help control HS by reducing body weight and improving patients' quality of life (DLQI 13 $\rightarrow$ 9). However, its effect on inflammatory markers and frequency of exacerbations was less pronounced. The rationale for using semaglutide in HS stems from its ability to reduce body weight and modulate metabolic and inflammatory pathways, which are strongly associated with the severity and progression of HS. These results suggest that se-

maglutide could be a useful adjunctive therapy in the treatment of HS, but further placebo-controlled trials are needed to confirm its efficacy [52].

Discussion

In recent years, there has been increasing interest in the use of GLP-1R agonists in the treatment of chronic inflammatory dermatoses, such as psoriasis and HS, which are often associated with pronounced metabolic dysfunction, due to their significant anti-inflammatory and immunomodulatory effects [2,9,25,38].

The expression of GLP-1 receptors in skin tissue and the presence of proglucagon peptides suggest that this signalling pathway may play a direct role in regulating inflammatory processes in the skin [9,25,32]. The GLP-1 signalling pathway can influence iNKT cell activity, which plays a key role in the pathogenesis of psoriasis [31]. Likewise, Buysschaert et al. reported a decrease in dermal $\gamma\delta$ T-lymphocytes, suggesting a possible direct effect of GLP-1R agonists on key effector cells in the pathogenesis of psoriasis [26].

Clinical studies and case reports indicate improvement of skin changes in patients with psoriasis associated with obesity and T2DM after the introduction of GLP-1R agonists such as exenatide, liraglutide and semaglutide [26,27,29,31,33]. However, the question arises as to the extent to which this effect is independent of the simultaneously achieved reduction in body mass, given the well-documented relationship between obesity and the severity of psoriasis [25]. However, individual cases of psoriasis worsening during *liraglutide* therapy have also been reported, indicating heterogeneity in response and the need for caution and individualisation of therapy [37].

When it comes to HS, interest in GLP-1R agonists has been driven by the strong association of this disease with obesity and metabolic syndrome [38]. Emerging evidence indicates the potential benefit of GLP-1R agonists, primarily through reductions in body mass

and systemic inflammation [4,36,38,51]. Clinical studies and case reports describe significant reductions in body weight and improvements in the clinical course of the disease in HS patients treated with liraglutide, and indicate improved subjective quality of life and reduced symptom severity during GLP-1R agonist therapy [36,50]. The finding that semaglutide can contribute to better disease control when used as adjuvant therapy in patients with severe obesity is particularly significant [51]. However, unlike psoriasis, evidence for hidradenitis suppurativa remains in its early stages and is largely based on observational data [4,50]. Nevertheless, the increased risk of psoriasis in these patients, and the shared pathophysiological mechanisms further justify the use of GLP-1R agonists in both diseases [38].

Although liraglutide and semaglutide are currently the only GLP-1 analogues used in HS, the potential for other GLP-1R agonists such as dulaglutide to produce similar effects warrants further investigation. Continued research is needed to fully determine the role of GLP-1 agonists in the treatment of HS [4].

Conclusion

Although psoriasis and hidradenitis suppurativa differ in clinical presentation, they share numerous characteristics as chronic inflammatory dermatoses, including common risk factors such as obesity, insulin resistance, and type 2 diabetes mellitus, similar underlying inflammatory mechanisms, and a substantial negative impact on quality of life.

Owing to their metabolic, anti-inflammatory, and immunomodulatory effects, glucagon-like peptide-1 receptor agonists represent a promising therapeutic option for inflammatory dermatoses. Their beneficial effects are attributable not only to weight loss but also to direct immunomodulatory effects, which may explain their efficacy independent of body weight reduction. Further randomised, placebo-controlled clinical trials are required to confirm their effectiveness.

References

1. Patino W, Thomas A, Jain S, Del Rosso JQ, Issa NT. A review of glucagon-like peptide-1 in dermatology. *J Clin Aesthet Dermatol.* 2025;18(3):42-50.
2. Yaribeygi H, Maleki M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Anti-inflammatory potentials of incretin-based therapies used in the management of diabetes. *Life Sci.* 2020;241:117152.
3. Pandey S, Mangmool S, Parichatikanond W. Multifaceted roles of GLP-1 and its analogs: a review on molecular mechanisms with a cardiotherapeutic perspective. *Pharmaceuticals (Basel).* 2023;16(6):836.
4. Krajewski PK, Zlotowska A, Szepietowski JC. The therapeutic potential of GLP-1 receptor agonists in the management of hidradenitis suppurativa: a systematic review of anti-inflammatory and metabolic effects. *J Clin Med.* 2024;13(21):6292.
5. Lee YS, Jun HS. Anti-inflammatory effects of GLP-1-based therapies beyond glucose control. *Mediators Inflamm.* 2016;2016:3094642.
6. Gribble FM, Reimann F. Metabolic messengers: glucagon-like peptide 1. *Nat Metab.* 2021;3(2):142-8.
7. Maselli DB, Camilleri M. Effects of GLP-1 and its analogs on gastric physiology in diabetes mellitus and obesity. In: Islam MS, editor. *Diabetes: from research to clinical practice. Advances in experimental medicine and biology vol 1307.* Cham: Springer; 2021. p.171-92.
8. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). *Mol Metab.* 2019;30:72-130.

9. List JF, He H, Habener JF. Glucagon-like peptide-1 receptor and proglucagon expression in mouse skin. *Regul Pept.* 2006;134(2-3):149-57.
10. Faurischou A, Pedersen J, Gyldenløve M, Poulsen SS, Holst JJ, Thyssen JP, et al. Increased expression of glucagon-like peptide-1 receptors in psoriasis plaques. *Exp Dermatol.* 2013;22(2):150-2.
11. Psilopanagioti A, Nikou S, Logotheti S, Arbi M, Char-toumpekis DV, Papadaki H. Glucagon-like peptide-1 receptor in the human hypothalamus is associated with body mass index and colocalizes with the anorexigenic neuropeptide nucleobin-din-2/nesfatin-1. *Int J Mol Sci.* 2022;23(23):14899.
12. King GL. The role of inflammatory cytokines in diabetes and its complications. *J Periodontol.* 2008;79(8 Suppl):1527-34.
13. Lee YS, Park MS, Choung JS, Kim SS, Oh HH, Choi CS, et al. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. *Diabetologia.* 2012;55(9):2456-68.
14. Al-Badri MR, Azar ST. Effect of glucagon-like peptide-1 receptor agonists in patients with psoriasis. *Ther Adv Endocrinol Metab.* 2014;5(2):34-8.
15. El-Sahar AE, Safar MM, Zaki HF, Attia AS, Ain-Shoka AA. Sitagliptin attenuates transient cerebral ischemia/reperfusion injury in diabetic rats: implication of the oxidative-inflammatory-apoptotic pathway. *Life Sci.* 2015;126:81-6.
16. Alharbi SH. Anti-inflammatory role of glucagon-like peptide-1 receptor agonists and its clinical implications. *Ther Adv Endocrinol Metab.* 2024;15:20420188231222367.
17. Niedźwiedz M, Skibińska M, Ciężyńska M, Noweta M, Czerwińska A, Krzyścin J, et al. Psoriasis and seasonality: exploring the genetic and epigenetic interactions. *Int J Mol Sci.* 2024;25(21):11670.
18. Patrick MT, Li Q, Wasikowski R, Mehta N, Gudjonsson JE, Elder JT, et al. Shared genetic risk factors and causal association between psoriasis and coronary artery disease. *Nat Commun.* 2022;13(1):6565.
19. Zhang M, Chen JL, Fan SW, Sun XY, Zhou YQ, Luo Y, et al. Epidemiology of hypertension in psoriasis: an analysis of trends from 2006 to 2023. *Psoriasis (Auckl).* 2025;15:443-53.
20. Milankov A, Pejakovic S. Body mass index and the anterior cruciate ligament – integrating mechanical and inflammatory mechanisms. *Med Pregl.* 2025;78(9-12):229-34.
21. Olbrich H, Kridin K, Zirpel H, Hernandez G, Sadik CD, Gaffal E, et al. Glucagon-like peptide-1 receptor agonists and reduced mortality, cardiovascular and psychiatric risks in patients with psoriasis: a large-scale cohort study. *Br J Dermatol.* 2026;194(1):59-66.
22. Yin T, Zhang T, Ma L. Immune-related hub genes and their role in psoriasis pathogenesis. *Sci Rep.* 2025;15(1):17765.
23. Li Y, Zhigiang Y. Interleukin-17 family and psoriasis. *China Journal of Leprosy and Skin Disease.* 2017;33(1):59-61.
24. Paschou IA, Sali E, Paschou SA, Psaltopoulou T, Nicolaidou E, Stratigos AJ. GLP-1RAs in patients with psoriasis. *Hormones (Athens).* 2025;24(2):291-3.
25. Haran K, Johnson CE, Smith P, Venable Z, Kranyak A, Bhutani T, et al. Impact of GLP-1 receptor agonists on psoriasis and cardiovascular comorbidities: a narrative review. *Psoriasis (Auckl).* 2024;14:143-52.
26. Buysschaert M, Tennstedt D, Preumont V. Improvement of psoriasis during exenatide treatment in a patient with diabetes. *Diabetes Metab.* 2012;38(1):86-8.
27. Costanzo G, Curatolo S, Busà B, Belfiore A, Gullo D. Two birds one stone: semaglutide is highly effective against severe psoriasis in a type 2 diabetic patient. *Endocrinol Diabetes Metab Case Rep.* 2021;2021(1):21-0007.
28. Malavazos AE, Meregalli C, Sorrentino F, Vignati A, Dubini C, Scravaglieri V, et al. Semaglutide therapy decreases epicardial fat inflammation and improves psoriasis severity in patients affected by abdominal obesity and type 2 diabetes. *Endocrinol Diabetes Metab Case Rep.* 2023;2023(3):23-0017.
29. Faurischou A, Knop FK, Thyssen JP, Zachariae C, Skov L, Vilsbøll T. Improvement in psoriasis after treatment with the glucagon-like peptide-1 receptor agonist liraglutide. *Acta Diabetol.* 2014;51(1):147-50.
30. Reid CT, Tobin AM, Ahern T, O'Shea D, Kirby B. Liraglutide in combination with acitretin for severe recalcitrant psoriasis. *Br J Dermatol.* 2013;169(1):230-1.
31. Ahern T, Tobin AM, Corrigan M, Hogan A, Sweeney C, Kirby B, et al. Glucagon-like peptide-1 analogue therapy for psoriasis patients with obesity and type 2 diabetes: a prospective cohort study. *J Eur Acad Dermatol Venereol.* 2013;27(11):1440-3.
32. Hogan AE, Tobin AM, Ahern T, Corrigan MA, Gaoatswe G, Jackson R, et al. Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis. *Diabetologia.* 2011;54(11):2745-54.
33. Xu X, Lin L, Chen P, Yu Y, Chen S, Chen X, et al. Treatment with liraglutide, a glucagon-like peptide-1 analogue, improves effectively the skin lesions of psoriasis patients with type 2 diabetes: a prospective cohort study. *Diabetes Res Clin Pract.* 2019;150:167-73.
34. Lin L, Xu X, Yu Y, Ye H, He X, Chen S, et al. Glucagon-like peptide-1 receptor agonist liraglutide therapy for psoriasis patients with type 2 diabetes: a randomized-controlled trial. *J Dermatolog Treat.* 2022;33(3):1428-34.
35. Faurischou A, Gyldenløve M, Rohde U, Thyssen JP, Zachariae C, Skov L, et al. Lack of effect of the glucagon-like peptide-1 receptor agonist liraglutide on psoriasis in glucose-tolerant patients: a randomized placebo-controlled trial. *J Eur Acad Dermatol Venereol.* 2015;29(3):555-9.
36. Nicolau J, Nadal A, Sanchis P, Pujol A, Nadal C, Mas-miquel L. Effects of liraglutide among patients living with psoriasis and obesity. *Med Clin (Barc).* 2023;161(7):293-6.
37. Nowowiejska J, Baran A, Flisiak I. The first case of psoriatic skin lesions exacerbation after liraglutide. *Pol Arch Intern Med.* 2023;133(7-8):16527.
38. Gau SY, Preclaro IAC, Wei JC, Lee CY, Kuan YH, Hsiao YP, et al. Risk of psoriasis in people with hidradenitis suppurativa: a systematic review and meta-analysis. *Front Immunol.* 2022;13:1033844.
39. Chu CB, Yang CC, Tsai SJ. Hidradenitis suppurativa: disease pathophysiology and sex hormones. *Chin J Physiol.* 2021;64(6):257-65.
40. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. *Metab Syndr Relat Disord.* 2015;13(10):423-44.
41. Witte K, Wolk K, Witte-Händel E, Krause T, Kokolakis G, Sabat R. Targeting metabolic syndrome in hidradenitis suppurativa by phytochemicals as a potential complementary therapeutic strategy. *Nutrients.* 2023;15(17):3797.
42. Phan K, Charlton O, Smith SD. Hidradenitis suppurativa and metabolic syndrome: systematic review and adjusted meta-analysis. *Int J Dermatol.* 2019;58(10):1112-7.
43. Hirt PA, Castillo DE, Yosipovitch G, Keri JE. Skin changes in the obese patient. *J Am Acad Dermatol.* 2019;81(5):1037-57.
44. Kromann CB, Ibler KS, Kristiansen VB, Jemec GB. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. *Acta Derm Venereol.* 2014;94(5):553-7.
45. Engin A. The definition and prevalence of obesity and metabolic syndrome. *Adv Exp Med Biol.* 2017;960:1-17.

46. Canard C, Diaz Cives A, Gaubil-Kaladjian I, Bertin E, Viguier M. Impact of bariatric surgery on hidradenitis suppurativa. *Acta Derm Venereol.* 2021;101(6):adv00471.

47. Kaleta KP, Nikolakis G, Hossini AM, Balthasar O, Almansouri D, Vaiopoulos A, et al. Metabolic disorders/obesity is a primary risk factor in hidradenitis suppurativa: an immunohistochemical real-world approach. *Dermatology.* 2022;238(2):251-9.

48. Fletcher JM, Moran B, Petrasca A, Smith CM. IL-17 in inflammatory skin diseases psoriasis and hidradenitis suppurativa. *Clin Exp Immunol.* 2020;201(2):121-34.

49. Mei J, Sun J, Wu J, Zheng X. Liraglutide suppresses TNF- α -induced degradation of extracellular matrix in human

chondrocytes: a therapeutic implication in osteoarthritis. *Am J Transl Res.* 2019;11(8):4800-8.

50. Jennings L, Nestor L, Molloy O, Hughes R, Moriarty B, Kirby B. The treatment of hidradenitis suppurativa with the glucagon-like peptide-1 agonist liraglutide. *Br J Dermatol.* 2017;177(3):858-9.

51. Gupta R, Cesar L, Micheletti R, Fang V. Patient-reported outcomes of glucagon-like peptide-1 agonists on hidradenitis suppurativa severity. *JAAD Int.* 2025;21:40-3.

52. Lyons D, Louly Nathan A, Pender E, Murray G, Smith C, Kirby B, et al. Semaglutide for weight loss in people with obesity as an adjunctive treatment for hidradenitis suppurativa: its impact on disease control and quality of life. *Br J Dermatol.* 2024;191(4):631-3.

Rad je primljen 19. V 2026.

Recenziran 25. VI 2026.

Prihvaćen za štampu 3. VIII 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:189-196.

ETHICAL CHALLENGES IN THE USE OF INFORMATION TECHNOLOGY AND ARTIFICIAL INTELLIGENCE IN HEALTHCARE PRACTICE

ETIČKI IZAZOVI PRIMENE INFORMACIONIH TEHNOLOGIJA I VEŠTAČKE INTELIGENCIJE U ZDRAVSTVENOJ PRAKSI

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Review article

Pregledni članak

UDK 614.253:004.8

<https://doi.org/10.2298/MPNS2608197V>

Abstract

The healthcare service delivery paradigm has undergone a radical shift and systemic transformation with the integration of information technology and artificial intelligence systems into clinical practice. While technological advancements in medicine are growing exponentially, critical analysis of ethical implications has yet to develop to a level that reflects their practical application. This paper aims to systematise and analyse key ethical challenges, with a particular focus on privacy, algorithmic bias, and accountability in the clinical environment. It places special emphasis on an inclusive perspective in developing assistive technologies, re-examining the “autonomy paradox” of end-users through the concept of participatory design. The study points to the need to establish a transdisciplinary dialogue and integrate user experience into the early stages of software solution development. In the concluding remarks, it is highlighted that ethical standardisation and protocol transparency are fundamental prerequisites for applying artificial intelligence in modern rehabilitation, grounded in core humanistic values.

Key words: Artificial Intelligence; Information Technology; Delivery of Health Care; Bioethics; Self-Help Devices; Rehabilitation; Persons with Disabilities

Sažetak

Paradigma pružanja usluga u zdravstvu proživela je radikalnu promenu i sistemsku transformaciju uvođenjem informacionih tehnologija i sistema veštačke inteligencije u praktičnu primenu. Dok tehnološki napredak u medicini raste eksponencijalno, kritička analiza etičkih implikacija nije dostigla nivo razvoja koji odražava stvarnu praktičnu primenu. Cilj ovog rada je sistematizacija i analiza ključnih etičkih izazova, sa posebnim fokusom na pitanja privatnosti, algoritamske pristrasnosti i odgovornosti u kliničkom okruženju. Poseban osvrt dat je inkluzivnoj perspektivi razvoja asistivnih tehnologija, gde se kroz koncept participativnog dizajna preispituje tzv. „paradoks autonomije“ krajnjih korisnika. Rad ukazuje na neophodnost uspostavljanja transdisciplinarnog dijaloga i integracije korisničkog iskustva u rane faze razvoja softverskih rešenja. U zaključnim razmatranjima ističe se da etička standardizacija i transparentnost protokola predstavljaju ključne preduslove za primenu veštačke inteligencije u savremenoj rehabilitaciji koja se zasniva na osnovnim humanističkim vrednostima.

Ključne reči: veštačka inteligencija; informacione tehnologije; pružanje zdravstvene zaštite; bioetika; uređaji za samopomoć; rehabilitacija; osobe sa invaliditetom

Introduction

In recent decades, the term “digital age”, referring to the era we live in, has become popular among the general public. We notice the effects of this epithet in the more frequent use of digital devices such as mobile phones, tablets and similar devices, and we trace its origin in the field of information technology (IT). The intensive development of this discipline has led to the creation of numerous models and systems, among which artificial intelligence systems are particularly important, allowing the “modern” person to have faster access to information, a faster process of communication, control of the environment and various other functions that facilitate daily functioning [1,2]. Cars that operate without a human driver, personal assistants that remind people to take their

medicine on time, and navigation devices with voice commands are just some practical examples of how technology improves an individual’s functioning in everyday life. A large number of these systems are under the umbrella of assistive technologies, that is, devices and means designed to improve the functioning of people with disabilities, and in recent years, the concept of the “mainstream” technology, i.e. “general” technologies for wider social use, has also gained increasing attention [3,4]. Although, in essence, means and systems of this kind were created with positive intent and for the purpose of promoting well-being, it is not negligible that, due to the interference of ethical values and principles, numerous questions begin to arise, such as: Does technology exclusively serve the well-being of the individual, or can it violate their rights, such as privacy and dignity? Is the use of

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Abbreviations

IT – information technology
 AI – artificial intelligence

personal data in digital systems always safe? Will the responsibility for a mistake be taken by humans or machines? To answer these questions, it is necessary to examine the role and perspectives of applying ethical principles developed within modern scientific thought and documented legal frameworks. By understanding ethical values in the context of IT and artificial intelligence (AI), it becomes possible to reach a consensus that ensures digital systems not only improve users' quality of life, but also respect fundamental human values and rights.

This work aims to analyse the key ethical challenges associated with applying IT and AI in health practice, with special reference to privacy, algorithmic bias, responsibility and inclusiveness in the development of assistive technologies as an important segment of modern rehabilitation approaches.

Ethical challenges and digital security

One of the key advantages of modern information technologies and AI systems is reflected in their ability to enable individualised and personalised access for users [2]. Today's technologies tend to create a unique approach to each user, bringing people into the sphere of the so-called "technological citizenship". This societal shift faces obstacles because legal frameworks governing access to and manipulation of individual information remain insufficiently regulated [1]. In a study examining the ethical challenges of using AI in university education, many respondents expressed concern about the privacy and security of personal data in these systems. More than half of the respondents believe that AI systems lack sufficient transparency [5].

Issues of bias, privacy, transparency and accountability were also identified as ethical dilemmas. AI bias implies a tendency to make decisions based solely on the data or models that were used to train it, which, ethically, violates the principle of fairness and increases the risk of errors when making decisions or generating new data. In healthcare, this kind of bias can affect diagnostic accuracy, treatment choices, health-risk assessments, and especially biomedical research. The lack of diversity in the data means algorithms generate precise results for the "dominant" population, while for less represented and/or marginalised groups, the risk of errors in diagnosis and health risk assessment increases. At the same time, highly developed and complex systems threaten the transparency of their functioning and, therefore, the responsibility they bear in the event of an error [6]. To reduce the possibility of

the aforementioned errors, researchers in the field have systematised nine ethical principles related to the application of IT and AI, which include: the principle of transparency and explainability, the principle of responsibility, the principle of privacy, the principle of security, the principle of human control of technology, the principle of promoting human values, the principle of sustainable development and the principle of professional responsibility [7]. Authors Resnik and Hosseini [8] proposed recommendations for the responsible use of AI systems, which, among other things, emphasise that researchers bear responsibility for managing AI errors and biases, and should transparently show how AI is used. In addition to the potential threats mentioned, and despite the numerous identified advantages of using AI, the "ethical risks" identified in research from 2025 are characterised as: loss of critical thinking, dependence on technology and homogenisation of ideas [9]. Generating inaccurate data and copyright infringement also present ethical challenges in AI applications [10].

Regulatory frameworks and national strategies

In recent years, a law concerning the protection of data privacy in the use of IT came into force in the Netherlands. The original form of the law posed a risk to citizens, who, after conducting referendums and protests aimed at harmonising the law with society's needs and in cooperation with responsible bodies, helped create a law that represents and protects ethical, and indeed human, rights. Gardenier et al. stated in 2024 that legal regulations should be adjusted and adaptable to modern "technological citizenship" and should meet society's needs and knowledge [1]. At the forefront of IT and AI regulations are ethical frameworks that have not yet been standardised and remain at the level of proposals and recommendations for implementation. An example is the "Ethical framework for the responsible use of generative AI", developed in 2024 [11]. Resnik and Hosseini [8] also emphasise the need for concrete guidelines and principles for using modern technologies, and for this purpose they propose a unique guide in which ethical principles are deeply integrated. In modern research on regulating the application of IT, especially AI, pedagogical, technological and legal ethical dimensions permeate the discussion. Lim et al. in their 2025 research [12] emphasised the prioritisation of explainability in the application of AI in the field of education. At the same time, the development of regulatory and ethical principles must be accompanied by the development of healthcare professionals' competencies, as the responsible use of AI requires an under-

standing of how these systems function, as well as their limitations and potential risks [13].

In the Republic of Serbia, the global universal standard for AI ethics proposed by UNESCO was adopted, and, from 2020 to 2025, preventive mechanisms for the ethical and safe application of AI, contained within the AI Development Strategy, were introduced. Within this universal standard, special attention is paid to the application of ethics in education, science, the economy, and state administration. In addition to the systematisation of ethical guidelines, and for the sake of standardising ethical values in this field, the national platform for AI created a questionnaire to check the fulfilment of the conditions from the mentioned ethical guidelines for the development, application and use of reliable and responsible AI [14].

Inclusive perspective of implementing AI

In addition to the above-mentioned moral dilemmas that have developed in parallel with the increasing accessibility and availability of AI systems, questions about autonomy, dignity and other humanistic values are especially complicated when the above is viewed through the prism of application in the context of working with people from sensitive social categories, which includes people with disabilities. Modern rehabilitation approaches for working with people with disabilities imply the application of assistive technologies, which can help maintain and strengthen a person's current level of functioning and increase their participation in life activities. Integrating "smart technologies" into assistive technology devices is not new; moreover, it is an essential component of high-tech assistive technology [3,4]. By pairing these two areas, numerous advantages are achieved, such as achieving an optimal level of independence, reducing the need for dependence on others, reducing the cost of therapeutic procedures and other related financial expenses, more accurate performance of diagnostic procedures and monitoring, as well as a whole range of positive clinical and functional outcomes that contribute to a holistic approach to the patient [15].

As the field of assistive technologies, and at the same time the field of AI and IT, developed intensively in recent years, the ethical aspect of the application of these tools began to gain a wider view, and many questions in this field remained unresolved. At first, it was noticed that people with disabilities, although they are the "end" users of assistive technology, are often excluded from the organisational teams that design the appearance, functionality, adaptability, and other characteristics of the particular device they develop. Such behaviour does not respect the

ethical principles that advocate inclusive access and equal participation. These principles emphasise the importance of the participation of individuals, future users of a particular service, in every phase of the process that concerns them personally. Failure to comply with ethical guidelines in this context can lead to the development of numerous devices intended for people with disabilities, which may not function as well as intended or at all, i.e. they do not respond to the real needs of people and which, as a result, are not used [15].

Another difficulty that may arise concerns the principle of autonomy. Wangmo et al., in their research from 2019, highlighted the problem of the "paradox of autonomy", thereby opening the issue of independence in decision-making. Although the primary goal of assistive technology is to ensure the highest possible level of independence, if a person uses an AI-based device such as a "smart" device, it can make decisions instead of the user (e.g., closing the door, turning off the alarm). Moreover, frequent software updates and changes that occur "in the background" in some cases do not include informed consent or present it inadequately to the person, which can potentially violate the user's essential right to self-determination and conscious control of the environment. In addition, the authors highlight the questionable status of confidentiality and data privacy [16].

A systematic literature review published in 2025 [17] indicates that, despite impressive technological progress, a "critical" gap remains between ethical principles and their practical application in rehabilitation. As stated in the research, it is necessary to focus on the psychosocial well-being of the "end" users, and also to strengthen respect for ethical principles through the introduction of protocol standardisation measures concerning the application of AI in the field of assistive technologies, especially with regard to the component of informed consent, as well as protocols for privacy protection.

Conclusion

The development of information technology and artificial intelligence brings numerous benefits to modern society, but it also poses serious ethical challenges related to privacy, transparency, fairness and responsibility. Research indicates that ethical principles and values must be integrated into all phases of development and application to ensure these systems do not threaten fundamental human rights and instead contribute to the well-being of users and society as a whole. Future development requires a transdisciplinary dialogue between engineers and

healthcare workers, with mandatory participation from technology users. Such an inclusive methodology is crucial for overcoming the gap between theoretical ethical principles and their effective application in clinical and rehabilitation practice. Existing

ethical frameworks and standards provide a strong basis for responsible, fair and reliable use of information technology and artificial intelligence in all areas of society and science.

References

1. Gardenier AM, van Est R, Royakkers L. Technological citizenship in times of digitization: an integrative framework. *Digit Soc.* 2024;3(2):21.
2. Levin I, Mamlok D. Culture and society in the digital age. *Information (Basel).* 2021;12(2):68.
3. Zallio M, Ohashi T. The evolution of assistive technology: a literature review of technology developments and applications. *arXiv [Preprint].* 2022:arXiv:2201.0712v1.
4. Golubović Š, Slavković S, Veselinović M. *Asistivne tehnologije.* Novi Sad: Medicinski fakultet Novi Sad; 2018.
5. Marín YR, Caro OC, Rituay AMC, Llanos KA, Perez DT, Bardales ES, et al. Ethical challenges associated with the use of artificial intelligence in university education. *J Acad Ethics.* 2025;23(4):2443-67.
6. Huriye AZ. The ethics of artificial intelligence: examining the ethical considerations surrounding the development and use of AI. *American Journal of Technology.* 2023;2(1):37-44.
7. Pflanzner M, Traylor Z, Lyons JB, Dubljević V, Nam CS. Ethics in human-AI teaming: principles and perspectives. *AI Ethics.* 2023;3(3):917-35.
8. Resnik DB, Hosseini M. The ethics of using artificial intelligence in scientific research: new guidance needed for a new tool. *AI Ethics.* 2025;5(2):1499-521.
9. Llerena-Izquierdo J, Ayala-Carabayo R. Ethics of the use of artificial intelligence in academia and research: the most relevant approaches, challenges and topics. *Informatics.* 2025;12(4):111.
10. Bjelobaba S, Waddington L, Perkins M, Foltýnek T, Bhat-tacharyya S, Weber-Wulff D. Research integrity and GenAI: a Rad je primljen 27. V 2026.
Recenziran 1. VII 2026.
Prihvaćen za štampu 7. VIII 2026.
BIBLID.0025-8105:(2026):LXXIX:7-8:197-200.
- systematic analysis of ethical challenges across research phases. *arXiv [Preprint].* 2024:arXiv:2412.10134.
11. Eacersall D, Pretorius L, Chugh R, Smirnov I, Spray E, Illingworth S, et al. Navigating ethical challenges in generative AI-enhanced research: the ETHICAL framework for responsible generative AI use. *Journal of Applied Learning and Teaching.* 2025;8(2):102-15.
12. Lim T, Gottipati S, Cheong M. What students really think: unpacking AI ethics in educational assessments through a triadic framework. *Int J Educ Technol High Educ.* 2025;22(1):56.
13. Javaid MK. Role of artificial intelligence in fracture liaison service setting. *Med Pregl.* 2025;78(1-2):7-9.
14. Nacionalna platforma za veštačku inteligenciju. *Etika u veštačkoj inteligenciji [Internet].* [cited 2026 Jan 11]. Available from: <https://www.ai.gov.rs/tekst/sr/238/etika-u-vestackoj-inteligenciji.php>
15. Vollmer Dahlke D, Ory MG. Emerging issues of intelligent assistive technology use among people with dementia and their caregivers: a U.S. perspective. *Front Public Health.* 2020;8:191.
16. Wangmo T, Lipps M, Kressig RW, Ienca M. Ethical concerns with the use of intelligent assistive technology: findings from a qualitative study with professional stakeholders. *BMC Med Ethics.* 2019;20(1):98.
17. Sasu JK, Ogunyemi AA, Quaicoe JS, Bauters M, Aheto SK. Ethics surrounding artificial intelligence-powered assistive technologies used by people with visual and hearing impairments: a systematic review. *Disabil Rehabil Assist Technol.* 2026;21(4):1092-117.

SEMINARS IN MEDICINE SEMINARI IZ MEDICINE

COMPARISON OF DENTAL AND SKELETAL MATURITY IN GIRLS FROM VOJVODINA

POREĐENJE DENTALNE I SKELETNE ZRELOSTI KOD DEVOJČICA U VOJVODINI

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Seminar in medicine

Seminar iz medicine

UDK 611.314:572.087

UDK 616.314-089.23-055.25

<https://doi.org/10.2298/MPNS2608201C>

Abstract

Introduction. Determining dental and skeletal maturity is highly important in planning orthodontic therapy. Due to possible discrepancies between dental and skeletal maturity, it is necessary to research this topic to improve orthodontic treatment. This study aimed to examine differences between dental and skeletal age of girls aged 9 to 11 years. **Material and Methods.** The study included medical records of 56 girls aged 9 to 11 years who were treated at the Department of Orthodontics, Clinic of Dental Medicine of Vojvodina. Dental age was determined using the Demirjian method on orthopantomographic images, while skeletal age was assessed using cephalometric radiographs by measuring cervical vertebrae. The results were statistically analysed for the entire sample and separately for age groups of 9, 10, and 11 years. Mean values, standard deviation, minimum and maximum values for chronological, dental, and skeletal age were calculated, along with statistical significance using the t-test. **Results.** A statistically significant difference between dental and skeletal maturity was found for the entire sample and for the 9- and 10-year age groups. For the 11-year age group, no statistically significant difference was observed. **Conclusion.** The results indicate that there is no consistent and reliable correlation between skeletal and dental maturity, which should be considered into account when planning orthodontic therapy.

Key words: Age Determination by Skeleton; Age Determination by Teeth; Child; Female; Orthodontics

Sažetak

Uvod. Precizna procena biološke zrelosti ima ključni značaj za pravilan izbor vremena i planiranje ortodontske terapije. Dentalna i skeletna starost predstavljaju najčešće korišćene pokazatelje, ali njihov međusobni odnos može varirati u zavisnosti od uzrasta i individualnih faktora. Cilj ovog istraživanja bio je da se ispita odnos između dentalne i skeletne starosti kod devojčica uzrasta od 9 do 11,9 godina u Vojvodini, kao i da se utvrdi postojanje statistički značajnih razlika između ovih parametara. **Materijal i metode.** Istraživanje je obuhvatilo medicinsku dokumentaciju 56 devojčica prosečnog uzrasta $10,7 \pm 0,92$ godine, lečenih na Odeljenju za ortopediju vilica Klinike za stomatologiju Vojvodine. Dentalna starost određena je *Demirjian* metodom na ortopantomografskim snimcima, dok je skeletna starost procenjena analizom trećeg i četvrtog cervikalnog pršljena na telerendgen snimcima. Statistička obrada obuhvatila je izračunavanje srednjih vrednosti, standardne devijacije i primenu t-testa za celokupan uzorak i pojedinačne starosne grupe (9, 10 i 11 godina). **Rezultati.** Prosečna hronološka, dentalna i skeletna starost iznosile su 10,27, 10,72 i 11,84 godine. Statistički značajna razlika između dentalne i skeletne starosti utvrđena je za celokupan uzorak ($p < 0,05$), kao i za uzraste od 9 i 10 godina. Kod jedanaestogodišnjakinja nije utvrđena statistički značajna razlika. Uočeno je smanjenje razlike između dentalne i skeletne starosti sa porastom uzrasta. **Zaključak.** Dentalna i skeletna starost nisu uvek u pouzdanoj korelaciji u mlađim uzrastima, što ukazuje na potrebu za individualnim pristupom u planiranju ortodontske terapije. U uzrastu oko 11 godina dentalna starost postaje pouzdaniji pokazatelj biološke zrelosti.

Ključne reči: skeletna starost; dentalna starost; dete; ženski pol; ortodoncija

Introduction

Timely and adequate orthodontic therapy has a significant impact on the growth and development of

Acknowledgement

The results presented in this paper are obtained in the framework of the project "Development and Application of Digital 3D Methods for the Fabrication of Dental Appliances", financed by the Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina. (Project number: 0038856804 2025 09418 003 000 000 001)

the entire orofacial system, as well as on the prevention of dental caries and periodontal disease. Understanding of the factors influencing growth is essential for proper diagnosis and timely, appropriate therapy [1].

Human growth begins at the moment of zygote formation and continues until approximately the age of 20, when active growth ceases. It is divided into two periods: prenatal and postnatal [1].

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During growth, there are phases of increased intensity. The most significant growth spurts occur during the foetal period, in the first year of life, and later during prepubertal and pubertal periods.

Development follows growth and is reflected not only in achieving adult size and proportions, but also in tissue composition and functional capacity of organs. Biological maturation may precede or lag behind chronological age.

Successful orthodontic therapy requires thorough knowledge of the growth and development of the orofacial system [2]. Determining the optimal timing for initiating orthodontic treatment is directly related to identifying periods of accelerated growth and evaluating individual growth potential. In orthodontics, treatment timing plays a crucial role in determining the approach to correcting jaw and tooth development [3].

Each child or adolescent has an individual growth rate influenced by factors such as heredity, nutrition, hormonal status, and environmental factors. Determining individual growth rate before orthodontic treatment is essential, as it significantly affects treatment success [4].

Chronological age represents the time elapsed from birth to the moment of assessment [2].

One of the most commonly used methods for assessing patient maturity is dental maturity, based on the degree of tooth calcification. This method is widely accepted because it shows less variation compared with methods for determining skeletal or sexual maturity [5]. Therefore, teeth are considered reliable biological indicators for assessing growth and development [5,6].

A strong correlation exists between tooth development and individual maturity [5–8].

The most commonly used method is the Demirjian method, developed in a French-Canadian population [7]. It evaluates the calcification stages of seven permanent teeth in the upper left quadrant for individuals up to 16 years of age.

Skeletal age, or bone maturity, is assessed from bone morphology and mineralisation. It is most commonly evaluated using hand-wrist radiographs and cervical vertebrae analysis [9]. Gnathometric analysis can also be used to assess the shape and development of the dental arches and jaws [10].

The development of cervical vertebrae follows a consistent pattern similar to other skeletal structures [11] and can be evaluated on lateral cephalograms [12].

In 1972, Lamparski introduced the use of cervical vertebrae for assessing skeletal maturity. He identified morphological characteristics visible on radiographs at different developmental stages and created a descriptive atlas. His method proved to be reliable,

valid, and clinically useful, comparable to hand-wrist radiography [13].

Hassel and Farman (1995), as well as Mito et al. (2002), further confirmed the reliability of cervical vertebrae analysis [12,14].

This study aimed to determine skeletal age in girls aged 9 to 11.99 years, compare it with dental maturity, and assess potential differences between skeletal and dental age across age groups.

We hypothesised that skeletal and dental age would correspond and that there would be no significant differences between them.

Material and Methods

The study was conducted at the Clinic of Dental Medicine of Vojvodina in December 2024. The sample consisted of medical records of 56 girls with a mean age of 10.27 ± 0.92 years (range: 9–11.99 years) who were treated at the Department of Orthodontics.

Participants were randomly selected from patient records. We used the most recent records available until we reached a total of 56 girls who met the inclusion criteria.

Inclusion criteria: Presence of the germs of all teeth; Visibility of the third and fourth cervical vertebrae on cephalograms; Age between 9.0 and 11.99 years

Exclusion criteria: Hypodontia; Hyperdontia; Cleft lip and palate; Congenital syndromes affecting the orofacial region (Apert, Crouzon, Treacher-Collins, etc.).

Dental maturity was assessed using the Demirjian method on orthopantomograms via the OnyxCeph software, which assigns scores based on developmental stages (A–H) of permanent teeth in the upper left quadrant.

Skeletal maturity was assessed by measuring anterior height (AH) and anteroposterior length (AP) of the third and fourth cervical vertebrae on cephalograms.

The formula used was:

Vertebral age = $1.3523 + 6.7691 \times AH3/AP3 + 8.6408 \times AH4/AP4$ [11]

Statistical analysis was performed using MS Excel 2007. Mean values, standard deviation, and minimum and maximum values were calculated for chronological, dental, and skeletal age. Differences were assessed using the t-test.

Results

The mean chronological age was 10.27 years, the mean dental age was 10.72 years, and the mean skeletal age was 11.84 years.

A statistically significant difference between skeletal and dental age was observed in the total sample.

The sample was divided into age groups:

9 years (9.0–9.99)

10 years (10.0–10.99)

11 years (11.0–11.99)

Dental age means:

9 years: 9.89

10 years: 11.16

11 years: 11.39

Skeletal age means:

9 years: 11.62

10 years: 12.09

11 years: 11.82

We found statistically significant differences between dental and skeletal age in the 9- and 10-year groups, but not in the 11-year group.

Discussion

Chronological age was expressed in years using a decimal system for statistical simplicity. Dental age was assessed using the Demirjian method, widely recognised in scientific research [2,4–8,11,15,16]. Skeletal age was determined using the Caldas method [15].

Skeletal age is considered a more reliable indicator of growth than chronological age [2,3].

A major advantage of cervical vertebrae analysis is that it does not require additional radiation exposure, unlike hand-wrist radiographs, since cephalograms are already part of routine orthodontic diagnostics.

Most studies focus on comparisons between chronological and dental or skeletal age, whereas fewer directly compare dental and skeletal maturity [2,4,16].

This study found no consistent correlation between dental and skeletal age. The greatest difference was observed in 9-year-olds, whilst a slightly smaller but still significant difference was observed in 10-year-olds. No significant difference was found in 11-year-olds.

In 9-year-olds, the difference reached up to 4 years (skeletal age higher), with a minimum of 2 months. In 10-year-olds, differences were similar, though dental maturity sometimes exceeded skeletal age by 2–8 months. In 11-year-olds, differences decreased to a negligible level. These findings align with studies by Macha et al., Palanisamy et al., Ramos et al., and Cortes et al. [2,4,5,16].

Dental age exceeded chronological age across all groups, consistent with previous findings [2,4,16]. This may reflect generational changes in growth, nutrition, and socioeconomic conditions, suggesting a need to update standard reference values.

The hypothesis was rejected because significant differences were found both overall and in younger age groups.

Conclusion

There is no consistent and reliable relationship between dental and skeletal age.

As age increases, the difference between them decreases. Around the age of 11, accelerated dental development occurs, making dental age a more reliable indicator.

Orthodontic treatment planning should always be individualised, taking into account both dental and skeletal age.

References

1. Marković M, editor. *Ortodoncija*. Beograd-Zagreb: Medicinska knjiga; 1988.
2. Macha M, Lamba B, Avula JSS, Mathineni S, Margana PHJS, Chitoori P. Estimation of correlation between chronological age, skeletal age and dental age in children: a cross-sectional study. *J Clin Diagn Res*. 2017;11(9):ZC01-4.
3. Khazaei M, Mollabashi V, Khotanlou H, Farhadian M. Automatic determination of pubertal growth spurts based on the cervical vertebral maturation staging using deep convolutional neural networks. *J World Fed Orthod*. 2023;12(2):56-63.
4. Arciniega Ramos NA, Ballesteros Lozano M, Meléndez Ocampo A. Comparative analysis between dental, skeletal and chronological age. *Revista Mexicana de Ortodoncia*. 2013;1(1):33-7.
5. Paz Cortés MM, Rojo R, Alía García E, Mourelle Martínez MR. Accuracy assessment of dental age estimation with the Willems, Demirjian and Nolla methods in Spanish children: comparative cross-sectional study. *BMC Pediatr*. 2020;20(1):361.
6. Shi L, Zhou Y, Lu T, Fan F, Zhu L, Suo Y, et al. Dental age estimation of Tibetan children and adolescents: comparison of Demirjian, Willems methods and a newly modified Demirjian method. *Leg Med*. 2022;55:102013.
7. Jain V, Chowdhry A, Sircar K, Kapoor P. Application of comprehensive chart for dental age estimation (DAEcc) based on Demirjian method using orthopantograms: a pilot study. *Forensic Sci Int Rep*. 2019;1:100017.
8. Han MQ, Jia SX, Wang CX, Chu G, Chen T, Zhou H, et al. Accuracy of the Demirjian, Willems and Nolla methods for dental age estimation in a northern Chinese population. *Arch Oral Biol*. 2020;118:104875.
9. Mourelle R, Barberia E, Gallardo N, Lucavechi T. Correlation between dental maturation and bone growth markers in paediatric patients. *Eur J Paediatr Dent*. 2008;9(1):23-9.
10. Puškar N, Puškar M, Vučinić P, Ivić S, Petrović Đ. Determination of dentoalveolar parameters in patients with progenia. *Med Pregl*. 2022;75(9-10):279-83.
11. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. *Hum Biol*. 1973;45(2):211-27.
12. Hassel B, Farman AG. Skeletal maturation evaluation using cervical vertebrae. *Am J Orthod Dentofacial Orthop*. 1995; 107(1):58-66.

13. Lamparski DG. Skeletal age assessment utilizing cervical vertebrae [Master of science thesis]. Pittsburgh: University of Pittsburgh; 1972. p. 151-5.

14. Mito T, Sato K, Mitani H. Cervical vertebral bone age in girls. *Am J Orthod Dentofacial Orthop.* 2002;122(4):380-5.

15. Caldas Mde P, Ambrosano GM, Haiter Neto F. New formula to objectively evaluate skeletal maturation using lateral cephalometric radiographs. *Braz Oral Res.* 2007;21(4):330-5.

16. Palanisamy V, Rao A, Shenoy R, Baranya SS. Correlation of dental age, skeletal age and chronological age among children aged 9-14 years: a retrospective study. *J Indian Soc Pedod Prev Dent.* 2016;34(4):310-4.

Rad je primljen 2. IV 2026.

Recenziran 7. V 2026.

Prihvaćen za štampu 13. V 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:201-204.

CASE REPORTS PRIKAZI SLUČAJEVA

MULTIFOCAL CAESAREAN SCAR ENDOMETRIOSIS WITH EXTENSIVE ABDOMINAL WALL INVOLVEMENT – A CASE REPORT

MULTIFOKALNA ENDOMETRIOZA U OŽILJKU NAKON CARSKOG REZA SA OPSEŽNIM ZAHVATANJEM TRBUŠNOG ZIDA – PRIKAZ SLUČAJA

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Case report
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UDK 618.14-002-089.888.61:617.55
<https://doi.org/10.2298/MPNS2608205J>

Abstract

Introduction. Caesarean scar endometriosis is a rare form of abdominal wall endometriosis that develops following caesarean delivery as a result of ectopic implantation of endometrial tissue within the surgical scar. Patients typically present with cyclic pain and a palpable abdominal wall mass, although diagnosis may be challenging because it resembles other abdominal wall lesions. **Case Report.** A 31-year-old woman presented with painful nodules located within a previous Cohen laparotomy scar. Symptoms began approximately one year after caesarean delivery and were strongly associated with menstruation. Ultrasonography demonstrated multiple heterogeneous lesions within the scar. Surgical exploration revealed multifocal endometriosis involving the skin, subcutaneous tissue and fascia. Complete excision of all visible lesions was performed. Histopathological examination confirmed abdominal wall endometriosis by demonstrating endometrial glands and stroma associated with haemorrhage, hemosiderin-laden macrophages, and fibrosis. The postoperative course was uneventful, and satisfactory wound healing was observed at the two-week follow-up visit. **Conclusion.** This case illustrates an uncommon presentation of caesarean scar endometriosis characterised by multifocal disease and extensive abdominal wall involvement. Caesarean scar endometriosis should be considered in women with cyclic pain and a mass arising within a previous caesarean section scar. Early recognition and complete surgical excision remain essential for definitive diagnosis and effective treatment.

Key words: Endometriosis; Cicatrix; Cesarean Section; Surgical Wound; Abdominal Wall; Postoperative Complications; Signs and Symptoms; Treatment Outcome

Introduction

Endometriosis is a chronic oestrogen-dependent inflammatory disease characterised by the presence of endometrial glands and stroma outside the uterine

Sažetak

Uvod. Endometrioza u ožiljku nakon carskog reza predstavlja retku formu endometrioze trbušnog zida koja se dovodi u vezu sa implantacijom endometrijalnog tkiva u operativni ožiljak tokom hirurške procedure. Najčešće se manifestuje cikličnim bolom i palpabilnom promenom u predelu ožiljka, dok multifokalna bolest sa zahvatanjem više slojeva trbušnog zida predstavlja neuobičajenu prezentaciju. **Prikaz slučaja.** Tridesetjednogodišnja pacijentkinja javila se zbog bolnih nodularnih promena u predelu ožiljka nakon prethodnog carskog reza. Tegobe su se javile približno godinu dana nakon operacije i bile su cikličnog karaktera, sa pogoršanjem tokom menstruacije. Pacijentkinja je navodila povremenu pojavu braonkaste sekrecije iz kožnih otvora na oba kraja ožiljka. Ultrazvučnim pregledom identifikovane su višestruke lezije u području ožiljka. Intraoperativno je utvrđena multifokalna endometrioza sa zahvatanjem kože, potkožnog tkiva i fascije, uz supfascijalno širenje prema levom m. rektusu abdominis, bez infiltracije mišićnih vlakana. Učinjena je široka ekscizija svih makroskopski vidljivih promena uz primarnu rekonstrukciju fascije. Histopatološka analiza potvrdila je prisustvo endometrijalnih žlezda i strome, uz krvarenje, hemosiderofage i fibrozne promene. Postoperativni tok protekao je uredno. **Zaključak.** Multifokalna endometrioza u ožiljku nakon carskog reza sa ekstenzivnim zahvatanjem trbušnog zida predstavlja retku kliničku manifestaciju bolesti. Prisustvo kožnih promena i ciklične sekrecije može ukazivati na dugotrajan i progresivan tok bolesti. Rano prepoznavanje ovog entiteta i potpuna hirurška ekscizija od ključnog su značaja za postavljanje definitivne dijagnoze i uspešno lečenje.

Ključne reči: endometrioza; ožiljak; carski rez; hirurška rana; trbušni zid; postoperativne komplikacije; znaci i simptomi; ishod lečenja

cavity [1]. It affects approximately 10% of women of reproductive age and most commonly involves pelvic structures including the ovaries, pelvic peritoneum, and uterosacral ligaments [1]. Although endometrio-

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Abbreviations

CSE	– caesarean scar endometriosis
PDS	– polydioxanone
CT	– computed tomography
MRI	– magnetic resonance imaging

sis predominantly affects pelvic structures, lesions may also occur at extra-pelvic sites [2].

Caesarean scar endometriosis (CSE) represents a rare form of abdominal wall endometriosis that develops within or adjacent to a previous caesarean section scar. The reported incidence ranges from 0.03% to 1.5% following caesarean delivery [3,4]. The most widely accepted pathogenetic mechanism is iatrogenic implantation of viable endometrial cells into the wound during uterine incision and closure, followed by hormonal stimulation and proliferation of the implanted tissue [4,5]. Consequently, symptom onset may occur months or even years after the initial surgical procedure [6].

Patients typically present with a painful palpable mass in the abdominal wall, frequently associated with cyclical exacerbation of symptoms during menstruation [4,7]. Despite its characteristic clinical features, CSE remains a diagnostic challenge and is commonly misdiagnosed as other abdominal wall lesions, including hernias, granulomas, abscesses, haematomas, and soft tissue tumours [3–7].

Ultrasonography is usually the first-line imaging modality, while computed tomography and magnetic resonance imaging may be useful in determining the extent of disease and involvement of deeper structures [3,5]. Definitive diagnosis relies on histopathological confirmation demonstrating endometrial glands and stroma within the affected tissue [3,6]. Complete surgical excision with clear margins remains the treatment of choice [3,5].

We present a case of multifocal caesarean scar endometriosis with involvement of the skin, subcutaneous tissue and fascia, successfully treated by wide surgical excision.

Case Report

A 31-year-old woman was referred to our department for elective surgical treatment of painful lesions located within a previous scar of Cohen laparotomy. The patient had undergone elective caesarean delivery approximately six years earlier because of the breech presentation of the foetus. One year and three months after surgery, she began experiencing pain localised to the scar region, which was strongly associated with her menstrual cycle and occasionally persisted beyond menstruation. The patient also reported cyclical brownish discharge from focal skin openings located at both lateral ends of the scar.



Figure 1. Preoperative appearance and localisation of palpable endometriotic lesions within the previous scar of Cohen laparotomy. In both corners of the incision, skin discolouration can be observed

Physical examination revealed multiple palpable nodules along the caesarean scar (**Figure 1**). Gynaecological examination was otherwise unremarkable. Preoperative ultrasonography identified multiple heterogeneous lesions within the caesarean section scar, including a dominant lesion measuring 45×20 mm and several smaller adjacent nodules. The uterus and adnexa appeared normal.

Based on the patient's history, cyclical symptoms, and imaging findings, caesarean scar endometriosis was suspected, and surgical treatment was scheduled.

Under general anaesthesia, exploration of the previous Cohen incision and complete excision of all visible endometriotic tissue was performed. Surgery began with an incision approximately 1 cm from the margin of the affected skin. Subcutaneous tissue around the endometriotic nodules was grasped with curved Pean forceps, cut with scissors and ligated when needed in multiple steps. This was done to precisely prepare the nodule so that there would not be a large defect in the abdominal wall. The same technique was used to separate the nodule from the fascia (rectus sheath), leaving a 1x5 cm fascial defect in the left half, through which the abdominal cavity was opened.

Intraoperatively, two endometriotic nodules were identified in the right half of the scar, forming a conglomerate approximately 40 mm in diameter with extension to the skin surface and an associated small cutaneous opening. An additional conglomerate measuring approximately 10 cm in diameter was identified in the left half of the scar and also showed signs of prior focal cutaneous drainage. Both lesions were firmly adherent to the fascia, while the left-sided lesion demonstrated subfascial extension towards the left rectus abdominis muscle, without involvement of the muscle fibres. Dense adhesions between the greater omentum and the anterior abdominal wall

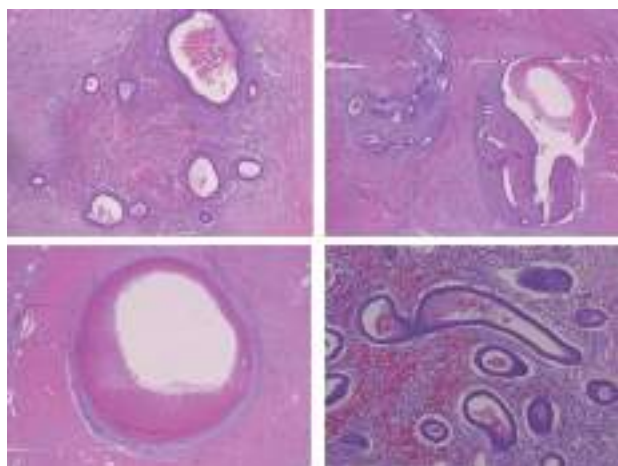


Figure 2. Resected surgical specimen following wide local excision of multifocal scar endometriosis

were also observed. The abdominal wall was subsequently reconstructed, and the surgical specimen was submitted for histopathological examination.

Macroscopic examination revealed two fragments of fibroadipose tissue measuring 11×4.5×4 cm and 6×3.5×3.5 cm (**Figure 2**). Histopathological analysis demonstrated endometrial glands lined by benign columnar epithelium surrounded by endometrial stroma, accompanied by areas of haemorrhage, haemosiderin-laden macrophages, and fibrotic scar tissue (**Figure 3**). These findings confirmed the diagnosis of abdominal wall endometriosis.

The postoperative course was uneventful. At the two-week follow-up visit, sutures were removed, and the surgical wound demonstrated satisfactory healing without signs of infection, wound dehiscence, or other early postoperative complications (**Figure 4**). The first menstrual period after the operation was painless. The patient was started on dienogest.

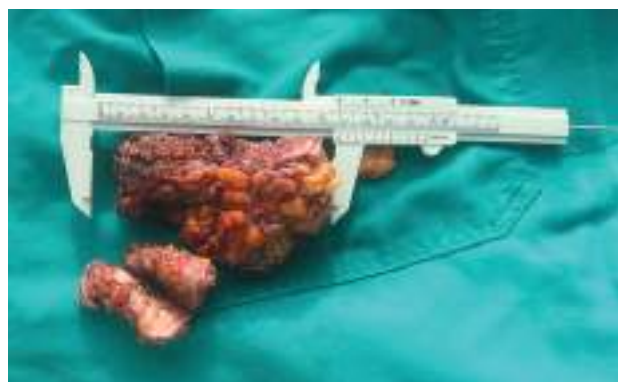


Figure 3. Histopathological examination demonstrating endometrial glands and stroma embedded within fibroadipose tissue, accompanied by haemorrhage and haemosiderin deposition (haematoxylin-eosin stain)



Figure 4. Postoperative appearance of the surgical wound at follow-up, demonstrating satisfactory healing by primary intention

Discussion

The present case demonstrated several features characteristic of caesarean scar endometriosis, including a history of caesarean delivery, cyclic pain, and multiple palpable lesions within the Cohen scar. However, unlike several reported cases describing a solitary lesion confined to the subcutaneous tissue or fascia [4,5,7], our patient exhibited multifocal disease with extensive involvement of the abdominal wall. Intraoperatively, multiple nodules were identified along the previous cesarean section scar, with extension into the fascia. Such extensive abdominal wall involvement may necessitate more complex surgical management [8]. Such extensive abdominal wall involvement may necessitate more complex surgical management and, in selected cases, abdominal wall reconstruction [8]. The extent of disease in our patient required wide excision involving the skin and subcutaneous tissue; however, the fascial defect was small and could be reconstructed with direct Polydioxanone (PDS) sutures.

Another notable finding was cutaneous involvement with signs of previous focal cutaneous drainage at both lateral ends of the incision, overlying the lesions. Cutaneous manifestations of abdominal wall endometriosis have been described in the literature [3,9]. Repeated cyclical haemorrhage and chronic inflammation within ectopic endometrial tissue may contribute to progressive tissue destruction and eventual breakdown of the overlying skin [1,2]. In our case, focal cutaneous involvement reflected the disease's chronic nature and highlighted the potential for progressive local tissue involvement when endometriotic lesions persist.

Cesarean scar endometriosis may pose a diagnostic challenge [8]. While the diagnosis was suspected preoperatively based on the patient's history and characteristic cyclic symptoms, the multifocal nature of the disease, cutaneous involvement, and extension into deeper abdominal wall structures emphasised the importance of thorough preoperative evaluation and careful surgical planning. Although the diagnosis was correctly suspected in our patient, similar le-

sions may mimic a variety of benign and malignant abdominal wall conditions, potentially leading to diagnostic uncertainty.

Imaging studies, particularly ultrasonography, play a key role in the initial evaluation of suspected scar endometriosis [9]. The diagnostic evaluation of endometriosis generally incorporates clinical findings and imaging, with surgical assessment used when indicated [10]. In the present case, ultrasonography successfully identified multiple lesions within the abdominal wall scar; however, intraoperative findings revealed more extensive disease than initially anticipated. This discrepancy highlights the limitations of ultrasonography in accurately assessing the full extent of deeply infiltrating abdominal wall endometriosis, particularly in patients with multifocal or complex lesions. In such cases, advanced cross-sectional imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), may provide a more comprehensive assessment of lesion size, infiltration depth, and involvement of adjacent structures, thereby facilitating preoperative planning [9]. Nevertheless, the availability and routine use of these modalities may be limited in certain clinical settings. Despite the important role of imaging, definitive diagnosis continues to rely on histopathological examination [3,6]. In our patient, the presence of endometrial glands and stroma associated with haemorrhage, haemosiderophages, and fibrosis confirmed the diagnosis.

Complete surgical excision remains the treatment of choice for caesarean scar endometriosis and is associated with a low recurrence rate [8]. Although hormonal therapies, including oral contraceptives, progestins, and gonadotrophin-releasing hormone ago-

nists, may provide temporary symptom relief, their effectiveness is generally limited by symptom recurrence after treatment discontinuation [9]. Consequently, medical therapy is typically reserved for selected patients or used as an adjunct to surgical management. In the present case, the extent of disease involvement required a wide local excision, resulting in an uncomplicated postoperative recovery. Overall, management should be individualised and based on a comprehensive assessment of clinical and imaging findings [10].

Several limitations should be acknowledged. Preoperative MRI or CT imaging was not performed, which may have provided a more precise evaluation of lesion extent and involvement of adjacent structures. In addition, the postoperative follow-up period was relatively short, limiting assessment of long-term recurrence. Finally, concomitant pelvic endometriosis could not be definitively excluded because dedicated pelvic imaging and laparoscopic assessment were not undertaken.

Conclusion

Caesarean scar endometriosis is an uncommon but important complication of caesarean delivery that should be considered in women presenting with cyclic pain and a palpable mass within or adjacent to a previous caesarean section scar. This case highlights the potential for multifocal disease with extensive involvement of the abdominal wall, including the skin and fascia. Early recognition and appropriate surgical management are essential to achieve definitive diagnosis and successful treatment while minimising the risk of progressive local extension and recurrence.

References

1. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. 2020;382(13):1244-56.
2. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *Lancet*. 2021;397(10276):839-52.
3. Masereka R, Kiyaka SM, Sikakulya FK. Endometriosis arising in a caesarean section scar: a case report. *Int J Surg Case Rep*. 2022;92:106862.
4. Elkhazein M, Ahmed S, Ahmed MB, Ismail MA, Mokhtar TH, Gurashi A, et al. Cesarean section scar endometriosis: a case report from Sudan. *Cureus*. 2025;17(8):e90368.
5. Al Shenawi H, Al Shenawi N, Al Mousa NA, Al Abbas LA, Al Zayer NM, Alqhtani MM, et al. A typical presentation of caesarean section scar endometriosis: a case report. *Cureus*. 2023;15(12):e49884.
6. Poudel D, Acharya K, Dahal S, Adhikari A. A case of scar endometriosis in cesarean scar: a rare case report. *Int J Surg Case Rep*. 2023;102:107852.
7. Al Hoshan MS, Shaikh AA. A classical case of cesarean scar endometriosis in a 35-year-old woman presenting with cyclical abdominal pain: a case report. *Am J Case Rep*. 2023;24:e940200-1.
8. Lopez-Soto A, Sanchez-Zapata MI, Martinez-Cendan JP, Ortiz Reina S, Bernal Mañas CM, Remezal Solano M. Cutaneous endometriosis: presentation of 33 cases and literature review. *Eur J Obstet Gynecol Reprod Biol*. 2018;221:58-63.
9. Gonzalez RH, Singh MS, Hamza SA. Cutaneous endometriosis: a case report and review of the literature. *Am J Case Rep*. 2021;22:e932493.
10. Bjelica A, Ćurčić J, Stajić D, Ilinčić M. Reproductive health screening for endometriosis, ovarian reserve, polycystic ovary syndrome and most common sexually transmitted diseases. *Med Pregl*. 2024;77(5-6):171-6.

Rad je primljen 24. VI 2026.

Recenziran 3. VIII 2026.

Prihvaćen za štampu 7. VIII 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:205-208.

A RARE GASTROINTESTINAL AND PANCREATIC IMMUNE-RELATED ADVERSE EVENT DURING PEMBROLIZUMAB THERAPY IN TRIPLE NEGATIVE BREAST CANCER – A CASE REPORT

REDAK SLUČAJ GASTROINTESTINALNE I PANKREATIČNE IMUNOPOSREDOVANE NEŽELJENE REAKCIJE TOKOM PRIMENE PEMBROLIZUMABA U LEČENJU TROSTRUKO-NEGATIVNOG KARCINOMA DOJKE – PRIKAZ SLUČAJA

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Case report

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UDK 618.19-006.6:615.277.3.065

<https://doi.org/10.2298/MPNS2608209N>

Abstract

Introduction. Immune checkpoint inhibitors have improved outcomes in triple-negative breast cancer but may trigger immune-related adverse events involving multiple organs. Pancreatic toxicity is uncommon but clinically important, and its recognition is challenging because of broad differential diagnoses. **Case Report.** We report the case of a 44-year-old woman with a first relapse of triple-negative breast cancer after seven years of disease-free follow-up. Germline testing revealed a mutation in the breast cancer susceptibility gene 1. First-line systemic therapy with pembrolizumab combined with weekly paclitaxel was initiated, resulting in a radiologically confirmed partial response. During the fifth treatment cycle, the patient developed upper abdominal discomfort, and endoscopy identified fibrin-covered “kissing” duodenal bulb ulcers, suggestive of possible immune-mediated duodenitis. Symptoms improved with proton pump inhibitors and supportive care. After reintroduction of therapy, the patient subsequently presented with recurrent symptoms. Laboratory evaluation revealed markedly elevated pancreatic enzymes, while imaging confirmed acute pancreatitis. Alternative aetiologies were excluded. Pembrolizumab was permanently discontinued, and corticosteroid therapy was initiated, resulting in gradual clinical and biochemical recovery. Maintenance therapy with a poly adenosine diphosphate-ribose polymerase inhibitor was introduced. At 10 months of follow-up, the patient remained asymptomatic, with preserved pancreatic function and sustained partial response. **Conclusion.** This case highlights an uncommon presentation of pembrolizumab-associated pancreatic and duodenal toxicity in a patient with triple-negative breast cancer. Awareness of rare irAEs is crucial to ensure timely diagnosis and effective management. Multidisciplinary collaboration and individualised therapeutic planning enabled both toxicity resolution and continued oncological disease control in this patient.

Key words: Breast Neoplasms; Triple-Negative Breast Neoplasms; Antibodies, Monoclonal, Humanized; Antineoplastic Agents, Immunological; Drug-Related Side Effects and Adverse Reactions; Gastrointestinal Diseases; Pancreatic Diseases; Immunotherapy; Immune Checkpoint Inhibitors; Patient Care Team

Sažetak

Uvod. Imunološki inhibitori kontrolnih tačaka značajno su unapredili ishode lečenja trostruko negativnog karcinoma dojke. Istovremeno njihova primena može izazvati neželjene događaje koji zahvataju više organskih sistema. Pankreatitis predstavlja retku, ali klinički relevantnu manifestaciju, čije prepoznavanje može biti otežano zbog nespecifičnih simptoma i širokog spektra diferencijalno-dijagnostičkih mogućnosti. **Prikaz slučaja.** Pacijentkinji starosti 44 godine, koja je nakon sedam godina remisije razvila prvi relaps trostruko negativnog karcinoma dojke, u lečenje je uvedena prva linija terapije pembrolizumabom u kombinaciji sa nedeljnim paklitakselom što je dovelo do radiološki potvrđenog parcijalnog odgovora. Germinativno testiranje potvrdilo je prisustvo mutacije gena predispozicije za karcinom dojke 1. Tokom petog ciklusa lečenja kod pacijentkinje se javljao bol u gornjem delu abdomena; endoskopijom su uočeni fibrinom prekriveni *kissing* ulkusi u bulbusu duodenuma, koji su ukazivali na imunoposredovani duodenitis i koji je saniran nakon primene inhibitora protonске pumpe. Nakon ponovnog uvođenja terapije registrovan je povratak simptoma. Laboratorijski nalazi pokazali su povišene pankreasne enzime, a radiološkim ispitivanjem potvrđen je akutni pankreatitis. Alternativni uzroci su isključeni. Pembrolizumab je trajno obustavljen i započeta je kortikosteroidna terapija koja je dovela do postepenog kliničkog i biohemijskog poboljšanja. Uvedena je terapija održavanja inhibitorom poliadenozin difosfat-riboza polimeraze. Nakon deset meseci praćenja, pacijentkinja je bez simptoma, sa očuvanom pankreasnom funkcijom i održanim parcijalnim odgovorom na primenjenu terapiju. **Zaključak.** Ovaj slučaj prikazuje pojavu pankreasne i duodenalne toksičnosti povezane sa primenom pembrolizumaba kod pacijentkinje sa karcinomom dojke. Poznavanje retkih imunoposredovanih neželjenih reakcija ključno je za pravovremeno prepoznavanje i adekvatno lečenje. Multidisciplinarni pristup i individualizovano planiranje terapije omogućili su istovremeno saniranje toksičnosti i kontrolu bolesti.

Ključne reči: tumori dojke; trostruko negativni tumori dojke; humanizovana monoklonska antitela; imunološki antineoplastični agensi; neželjena dejstva i neželjene reakcije povezane sa lekovima; gastrointestinalne bolesti; bolesti pankreasa; imunoterapija; inhibitori imunskih kontrolnih tačaka; multidisciplinarni tim

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Abbreviations

BRCA1	– breast cancer susceptibility gene 1
CTCAE	– common terminology criteria for adverse events
CPS	– combined positive score
EGDS	– oesophagogastrroduodenoscopy
ER	– oestrogen receptor
HER-2	– human epidermal growth factor receptor 2
ICI	– immune checkpoint inhibitor
irAE	– immune-related Adverse Event
MRI	– magnetic resonance imaging
MSCT	– multislice computed tomography
PARP	– poly (adenosine diphosphate-ribose) polymerase
PD-1	– programmed Cell Death Protein 1
PD-L1	– Programmed Death Ligand 1
PPI	– proton pump inhibitor
PR	– progesterone receptor
RECIST	– Response Evaluation Criteria in Solid Tumours
TNBC	– triple-negative breast cancer
NCCN	– National Comprehensive Cancer Network Guidelines

Introduction

Immune checkpoint inhibitors (ICIs) are immunomodulatory immunoglobulin-based agents designed to restore antitumour T cell activity by targeting inhibitory immune checkpoint pathways, most commonly programmed death receptor-1 (PD-1), programmed death ligand-1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and have revolutionised cancer care. More recently, lymphocyte activation gene-3 (LAG-3) has also emerged as a clinically validated checkpoint target, while other inhibitory receptors such as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), V-domain Ig suppressor of T-cell activation (VISTA), B- and T-lymphocyte attenuator (BTLA), T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) remain under active investigation [1]. In this report, we focus on pembrolizumab, an anti-PD-1 antibody, because it was the agent used in our patient. However, activating the immune system through ICIs results in a high burden of toxicities, known as immune-related adverse events (irAEs), which can become chronic and even life-threatening [2,3]. Among breast cancer subtypes, triple-negative breast cancer (TNBC) that is defined by the absence of oestrogen (ER) and progesterone (PR) receptor expression, as well as the lack of human epidermal growth factor receptor 2 (HER-2) overexpression or amplification and frequently high proliferative activity commonly assessed by the Ki-67 index, remains one of the most challenging to treat due to its intrinsic genomic instability, common association with germline BRCA mutations, lack of actionable receptor targets, and typically aggressive clinical behaviour [4,5]. Over the past several years, integrating PD-1/PD-L1 blockade has opened a new therapeutic avenue

for selected patients with early-stage and metastatic TNBC, offering the potential for improved survival in disease settings where progress had long been marginal [4,6]. As the use of ICIs expands in routine clinical practice, recognition of their distinct toxicity profile has become increasingly important, particularly given the potential for immune-mediated effects to involve nearly any organ system [3,7,8]. Similarly, rare oncological presentations and atypical clinical manifestations remain diagnostically challenging and are best documented through carefully reported case reports and literature reviews [9]. We report a rare case of acute pancreatitis accompanied by “kissing” duodenal bulb ulcers arising as an irAE of pembrolizumab therapy. This unusual presentation expands the spectrum of gastrointestinal toxicity associated with ICIs and emphasises the importance of early recognition and tailored multidisciplinary management.

Case Report

A 44-year-old female patient was diagnosed with a first relapse of previously treated invasive ductal carcinoma, triple-negative phenotype (ER 0, PR 0, HER-2: immunohistochemistry score 2+ with negative dual silver in situ hybridisation (dualSISH-), Ki67 30%). After 7 years of follow-up, a first local relapse with observed capsular and muscular infiltration, and supraclavicular and parasternal lymphadenopathy was detected. Core-needle biopsy reconfirmed the triple-negative phenotype (invasive ductal carcinoma, ER 0, PR 0, HER-2: 2+, dualSISH-, Ki67 45%, PD-L1 positive with a combined positive score (CPS status: ≥ 10)). At the same time, additional testing identified presence of the germline BRCA1 mutation. Therefore, the first-line systemic treatment with pembrolizumab in combination with weekly paclitaxel was introduced according to multidisciplinary tumour board recommendation. The first three initial cycles were well tolerated, with a registered partial response on multislice computed tomography (MSCT) per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1 PR). During the fifth cycle, the patient reported upper abdominal discomfort with dyspeptic symptoms. There was no history of prolonged or regular nonsteroidal anti-inflammatory drug use before symptom onset. Oesophagogastroduodenoscopy (EGDS) revealed hyperaemic and oedematous duodenal mucosa with fibrin-covered kissing ulcers in the duodenal bulb, which do not strongly support, yet are not incompatible with immune-mediated duodenitis. Further diagnostics showed a negative *Helicobacter pylori* test. Symptom-oriented treatment was initiated, including proton-



Figure 1. T2 blade FS sequence: abdominal MRI demonstrates diffuse enlargement and T2 hyperintensity of the pancreatic head and body with surrounding inflammatory fat stranding and small volume peripancreatic fluid, without biliary duct dilation

pump inhibitors (PPIs) and mucosal protective agents, with gradual clinical improvement. After a one-month interruption in antineoplastic treatment, combined immuno-chemotherapy was reinitiated for one additional cycle, after which ICI monotherapy was continued with close monitoring. After the seventh cycle, the patient presented with recurrent epigastric pain, nausea and anorexia but remained haemodynamically stable, with preserved renal function and no evidence of respiratory compromise. Laboratory testing revealed markedly elevated serum lipase 533 U/L (8-57 U/L) and pancreatic amylase 303 U/L (27-102 U/L), complemented by imaging findings (abdominal MRI demonstrated diffuse enlargement and T2 hyperintensity of the pancreatic head and body with surrounding inflammatory fat stranding and small volume peripancreatic fluid, without biliary duct dilation) consistent with acute pancreatitis (**Figure 1**). There was no prior history of gallstone disease, alcohol use, hypertriglyceridaemia or other secondary causes, suggesting a high likelihood of immune-mediated aetiology. According to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) and the National Comprehensive Cancer Network Guidelines (NCCN), the patient developed grade 3 immune-related pancreatitis. In accordance with irAE management guidelines, pembrolizumab was discontinued. An EGDS showed, which showed no signs of recurrent or active duodenal ulceration. Systemic corticosteroids (methylprednisolone 0.5 mg/kg/day) were commenced, followed by the transition to oral prednisone once grade 1, <3x ULN (CTCAE v5.0) pancreatic enzyme levels were attained, with a gradual taper of 5 mg per week over approximately 1 month in consultation with gastroenterology/pancreatic subspecialist. Supportive symptomatic care included analgesia, intravenous hydration, bowel rest and continuous proton pump inhibitors (PPIs). Over the following four months, pancreatic enzyme values steadily normalised, with full clinical recovery and

resolution of abdominal symptoms. Due to the severity of the immune-related pancreatic toxicity, immunotherapy was not reintroduced. Given the presence of a BRCA1 Mutation, poly (ADP-ribose) polymerase (PARP) inhibitors were instituted as maintenance therapy. At the most recent follow-up, 10 months after PARPi initiation, the patient remained clinically stable and asymptomatic from a gastrointestinal standpoint, with laboratory parameters within reference ranges. From the oncological perspective, the previously achieved RECIST 1.1 PR was sustained.

Discussion

TNBC represents an aggressive breast cancer subtype with limited targeted therapeutic options and generally poorer clinical outcomes [4,5]. The incorporation of ICIs has reshaped the therapeutic paradigm for metastatic TNBC. In particular, the phase III KEYNOTE-355 trial showed that adding pembrolizumab to chemotherapy significantly improves progression-free and overall survival in patients whose tumours express PD-L1 with CPS ≥ 10 . CPS represents the ratio of PD-L1 positive tumour and immune cells to the total number of viable tumour cells and is used as a predictive biomarker for immunotherapy response in TNBC, thereby establishing pembrolizumab plus chemotherapy as a standard first-line regimen in appropriately selected patients [4-6]. This combination was adopted into routine clinical practice in Serbia in 2024, aligning national treatment standards with contemporary international guidelines. Pembrolizumab exerts antitumour effects by blocking PD-1 on activated T lymphocytes, restoring anti-tumour immune surveillance. However, by enhancing immune activation, PD-1 inhibition can also disrupt peripheral tolerance, leading to a spectrum of irAEs [2,3,7,8]. The present case illustrates several clinically important aspects of ICI-associated GI toxicity. First, the patient achieved a sustained partial oncological response to pembrolizumab-based therapy, consistent with data from the KEYNOTE-355 trial demonstrating clinical benefit in PD-L1 positive TNBC with CPS ≥ 10 . Tumour response was assessed using RECIST 1.1 criteria, consistent with the response assessment methodology used in the KEYNOTE-355 study [4]. However, despite favourable tumour control, treatment was complicated by sequential upper gastrointestinal (GI) and pancreatic irAEs, highlighting the complex balance between antitumour efficacy and immune-mediated toxicity during PD-1 blockade. Gastrointestinal (GI) toxicities such as colitis and hepatitis are well-recognised, whereas immune-mediated pancreatic involve-

ment is relatively uncommon but clinically significant. Recent reports also highlight the duodenum as a possible site of immune-related injury, with histology demonstrating villous blunting and intraepithelial lymphocytosis. Such upper-small-intestinal involvement underscores the need to broaden clinical vigilance beyond typical enterocolitis, particularly when patients under ICI present with epigastric pain or upper GI symptoms [10,11]. The estimated incidence of immune-related pancreatic enzyme elevation with PD-1 inhibitors is approximately 1–2%, and clinically overt pancreatitis is reported in ~1–2% of cases [7,8]. Pharmacovigilance registry data indicate a median symptoms onset within the first 2–3 months of treatment and a non-negligible risk of morbidity [7,8]. Mechanistically, ICI-induced pancreatitis is driven by the activation and clonal expansion of cytotoxic T-cells with loss of tolerance to pancreatic self-antigens. This leads to T-cell infiltration of pancreatic parenchyma, cytokine-mediated acinar cell damage, and premature activation of digestive enzymes, resulting in pancreatic autodigestion [7,8,12]. In the present case, the clinical course was consistent with this immune-driven pathology, according to CTCAE v5.0 criteria and NCCN guideline, the patient developed grade 3 immune related pancreatitis with significant pancreatic enzyme elevation and radiologically confirmed pancreatic inflammation, evidenced by the absence of classical aetiological factors (gallstones, alcohol, hypertriglyceridaemia) and the favourable response to systemic corticosteroids, with subsequent complete clinical and biochemical recovery [13–15]. An additional dimension in this case is the presence of a germline BRCA1 mutation. BRCA1-associated TNBC is characterised by heightened genomic instability, increased neoantigen load, and elevated tumour-infiltrating lymphocytes, fea-

tures that contribute to enhanced intrinsic immunogenicity [16–18]. Although current data do not demonstrate increased irAE risk in BRCA1 mutation carriers, a more immune-reactive tumour microenvironment could plausibly contribute to amplified immune activation during ICI therapy, potentially explaining the severity of pancreatic toxicity observed in this patient [16]. Following guideline-based management, pembrolizumab was permanently discontinued due to the development of grade ≥ 3 pancreatitis, while chemotherapy was temporarily held and later resumed [13–15]. The transition to maintenance therapy with a PARP inhibitor represented an evidence-based (supported by the OlympiAD trial) and biologically rational continuation strategy, given the patient's BRCA1 mutation [19]. Notably, the partial radiological response achieved during pembrolizumab-based therapy was sustained throughout follow-up, consistent with emerging evidence suggesting that irAEs may be associated with more durable antitumour immune responses [20].

Conclusion

This case underscores the importance of prompt recognition and management of immune-related pancreatic toxicity during immune checkpoint inhibitor therapy, particularly as these agents become increasingly integrated into triple-negative breast cancer treatment pathways. While rare, pancreatitis must be considered in patients presenting with upper abdominal pain, dyspepsia, or unexplained pancreatic enzyme elevation during immunotherapy. Close multidisciplinary collaboration between oncology and gastroenterology teams is essential to ensure timely diagnosis, appropriate corticosteroid administration, and safe treatment modification.

References

1. Andrews LP, Yano H, Vignali DAA. Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: breakthroughs or backups. *Nat Immunol.* 2019;20(11):1425–34.
2. Martins F, Sofiya L, Sykietis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol.* 2019;16(9):563–80.
3. Wan G, Chen W, Khatib S, Roster K, Nguyen N, Yan B, et al. Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: a retrospective multicohort study. *Lancet Oncol.* 2024;25(8):1053–69.
4. Cortes J, Rugo HS, Cescon DW, Im SA, Yusof MM, Gallardo C, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med.* 2022;387(3):217–26.
5. Garrido-Castro AC, Lin NU, Polyak K. Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment. *Cancer Discov.* 2019;9(2):176–98.
6. Simmons CE, Brezden-Masley C, McCarthy J, McLeod D, Joy AA. Positive progress: current and evolving role of immune checkpoint inhibitors in metastatic triple-negative breast cancer. *Ther Adv Med Oncol.* 2020;12:1758835920909091.
7. Shatila M, Zhang HC, Shirwaikar Thomas A, Machado AP, Naz S, Mittal N, et al. Systematic review of immune checkpoint inhibitor-related gastrointestinal, hepatobiliary, and pancreatic adverse events. *J Immunother Cancer.* 2024;12(11):e009742.
8. Tong L, Yuan Y, He W, Yang W, Pan X. Adverse events associated with acute pancreatitis caused by immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. *Expert Opin Drug Saf.* 2025:1–9.
9. Marjanović M, Đurić A, Radić J, Petrović N, Stanulović N, Ignjatović Kresoja M. Large bowel obstruction due to metastasis of pancreatic cancer – case report and literature review. *Med Pregl.* 2024;77(9–12):331–7.

10. Johncilla M, Grover S, Zhang X, Jain D, Srivastava A. Morphological spectrum of immune check-point inhibitor therapy-associated gastritis. *Histopathology*. 2020;76(4):531-9.

11. Wang Q, Yu M, Zhang S. Peptic ulcer induced by immune checkpoint inhibitors successfully treated with glucocorticoids: a report of three cases and a literature review. *Exp Ther Med*. 2024;28(5):410.

12. Shirwaikar Thomas A, Chari ST. Immune checkpoint inhibitor-induced (Type 3) autoimmune pancreatitis. *Curr Gastroenterol Rep*. 2023;25(10):255-9.

13. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) Version 5.0. Bethesda, MD: U.S. Department of Health and Human Services; 2017.

14. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, Version 1.2020. *Natl Compr Canc Netw*. 2020;18(3):230-41.

15. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunothera-

py: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(Suppl 4):iv119-42.

16. Zhou Z, Li M. Evaluation of BRCA1 and BRCA2 as indicators of response to immune checkpoint inhibitors. *JAMA Netw Open*. 2021;4(5):e217728.

17. Fu X, Tan W, Song Q, Pei H, Li J. BRCA1 and breast cancer: molecular mechanisms and therapeutic strategies. *Front Cell Dev Biol*. 2022;10:813457.

18. Xu J, Bao H, Wu X, Wang X, Shao YW, Sun T. Elevated tumor mutation burden and immunogenic activity in patients with hormone receptor-negative breast cancer. *Oncol Lett*. 2019;18(1):449-58.

19. Indini A, Di Guardo L, Cimminiello C, Prisciandaro M, Randon G, De Braud F, et al. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. *J Cancer Res Clin Oncol*. 2019;145(2):511-21.

20. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-33.

Rad je primljen 8. XI 2025.

Recenziran 9. VIII 2026.

Prihvaćen za štampu 9. VIII 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:209-213.

SEMINAR FOR PHYSICIANS SEMINAR ZA LEKARE U PRAKSI

CYBERSECURITY IN CLINICAL PRACTICE

SAJBER BEZBEDNOST U KLINIČKOJ PRAKSI

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Seminar for physicians
Seminar za lekare u praksi
UDK 614.2:[004.8:004.056.5
<https://doi.org/10.2298/MPNS2608215B>

Abstract

Introduction. The digitalisation of healthcare systems has led to a rapid proliferation of cybersecurity threats that directly affect everyday clinical practice. Electronic health records, networked medical devices, and telemedicine platforms have become integral to modern medicine while simultaneously representing potential attack surfaces. Clinicians make daily decisions with data security implications, and inadequate training leaves them particularly vulnerable. **Threats and vulnerabilities.** Ransomware attacks that paralyse hospital systems, phishing campaigns targeting clinical staff, attacks on medical *Internet of Things* devices, and software supply chain compromise are the most prevalent threats in the contemporary healthcare environment. Each carries direct consequences for patient safety and continuity of care. **Clinician roles and advanced technologies.** Clinical staff represent both the most frequent point of system compromise and the most important line of defence. Advanced technologies including artificial intelligence based threat detection, blockchain data integrity, and federated learning offer emerging solutions, but require strategic institutional commitment for successful deployment. **Conclusion.** Cybersecurity is not exclusively an information technology matter – it is an integral component of medical ethics and responsibility towards patients. Its routine integration into clinical practice requires education, clear institutional procedures, and adequate resources.

Key words: Computer Security; Clinical Medicine; Electronic Health Records; Confidentiality; Ethics, Medical; Patient Rights

Introduction

Modern clinical practice – from reproductive medicine to cardiology, oncology and primary care – depends fundamentally on digital infrastructure: electronic health record (EHR), picture archiving and communication systems (PACS), internet-connected infusion pumps, patient monitors, telemedicine platforms, and mobile health applications. Each of these systems represents both a clinical asset and a potential point of vulnerability. Healthcare organisations

Sažetak

Uvod. Digitalizacija zdravstvenih sistema donela je sa sobom brzo širenje sajber pretnji koje direktno utiču na svakodnevnu kliničku praksu. Elektronski zdravstveni kartoni, medicinski uređaji povezani na mrežu i telemedicinske platforme postali su sastavni deo savremene medicine, ali i potencijalne mete kibernetičkih napada. Klinički lekari svakodnevno donose odluke s implikacijama za bezbednost podataka, a nedostatak obuke iz ove oblasti čini ih posebno ranjivim. **Pretnje i ranjivosti.** Ransomware napadi koji parališu bolničke sisteme, phishing poruke usmerene ka kliničkom osoblju, napadi na medicinske *Internet of Things* uređaje i kompromitovanje lanaca snabdevanja softverom najčešće su pretnje u savremenom zdravstvenom okruženju. Svaka od ovih pretnji nosi direktne posledice po bezbednost pacijenata i kontinuitet zdravstvene zaštite. **Uloga kliničara i napredne tehnologije.** Klinički lekari predstavljaju i najčešću tačku prodora napada i najvažniju liniju odbrane. Napredne tehnologije poput veštačke inteligencije za detekciju pretnji, blockchain integriteta podataka i federativnog učenja nude nova rešenja, ali zahtevaju stratešku podršku institucija. **Zaključak.** Sajber bezbednost nije isključivo IT pitanje – ona je sastavni deo medicinske etike i odgovornosti prema pacijentima. Njena rutinska primena u kliničkoj praksi zahteva edukaciju, jasne institucionalne procedure i odgovarajuće resurse.

Ključne reči: sajber bezbednost; klinička medicina; elektronski zdravstveni kartoni; poverljivost; medicinska etika; prava pacijenata

are among the most attractive targets for malicious actors, owing to the high market value of patient data, the operational criticality of services that cannot be interrupted, and the comparatively immature state of security governance in many institutions [1].

The scale of the problem has grown consistently over the past decade. Annual survey data from HIMSS and Proofpoint-Ponemon document that a substantial majority of healthcare organisations experienced significant security incidents in the preceding twelve months [2,3]. Data breaches in health systems cause

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Abbreviations

EHR	- electronic health record
PACS	- picture archiving and communication systems
GDPR	- General Data Protection Regulation
HIPAA	- Health Insurance Portability and Accountability Act
HITECH	- Health Information Technology for Economic and Clinical Health
AI	- artificial intelligence
IT	- information technology
IoMT	- Internet of Medical Things
MFA	- multi-factor authentication
EDR	- endpoint detection and response

damage on three simultaneous fronts: financial losses averaging millions of dollars per incident, reputational harm affecting patient trust, and direct clinical consequences, including delayed diagnoses, cancelled surgical procedures, and impaired access to medication records [2,3]. A systematic review published in *Cluster Computing* confirmed that breach-related disruption in healthcare is not merely a data governance concern but a patient safety issue of the first order [4].

Despite the severity of this threat, clinicians remain insufficiently prepared. Research conducted among practising physicians demonstrates that many are uncertain about their institutional security responsibilities and lack confidence in identifying or reporting incidents [5]. Training in cybersecurity across healthcare organisations remains ad hoc, inconsistently delivered, and rarely contextualised for clinical workflows [6].

Current threat landscape

Ransomware – malicious software that encrypts organisational data and demands payment for its release – represents the most operationally disruptive threat currently facing healthcare institutions. In clinical settings, the consequences are acute: patient management systems, laboratory results, radiology archives, and medication records can be rendered inaccessible for hours or days. Attacks of this type have been associated with measurable increases in patient mortality, particularly in emergency medicine and intensive care units where real-time data access is clinically indispensable. Both the HIMSS and Proofpoint-Ponemon reports rank ransomware among the top security concerns across health systems of all sizes [2,3], and the economic incentive for attackers is clear: healthcare organisations are less able to tolerate prolonged downtime than commercial enterprises, making them more likely to pay ransoms [4].

Phishing – the use of deceptive communications to extract credentials or deliver malware – remains the most common initial attack vector against healthcare systems [6,8]. Clinical staff are specifically vul-

nerable: high volumes of external communication, significant time pressure, and a professional culture that rewards rapid response all increase susceptibility. Healthcare systems are exposed to evolving cyber threats, including sophisticated phishing and social engineering attacks. At the same time, studies highlight persistent gaps in cybersecurity awareness and training among clinicians, which may hinder the identification of malicious communications [6,7].

The Internet of Medical Things (IoMT) – infusion pumps, defibrillators, implantable cardiac monitors, continuous glucose monitors, and bedside patient monitors connected to hospital networks – has created an attack surface that did not exist a decade ago. Many of these devices were designed before modern security standards existed, run legacy operating systems, and cannot receive software patches [7]. Deb et al., in a 2025 taxonomy of real-world IoMT attacks, documented incidents involving data interception, denial-of-service attacks targeting clinical devices, and, in adversarial research settings, unauthorised control of device function. ElSayed et al. proposed a lightweight adaptive machine-learning framework (CryptoDNA) for detecting distributed denial-of-service attacks in medical IoT environments, demonstrating that tailored artificial intelligence (AI)-based defences can address threats that generic security software does not cover [8]. Mohamadi et al. similarly showed that convolutional neural network models can detect known and novel threat types in IoMT networks at performance levels suitable for real-time deployment [9]. The clinical implication is unambiguous: a compromised medication-delivery device or patient monitor is not an IT problem – it is a patient safety incident.

Medical devices incorporating AI introduce a further category of risk. Mitra et al. demonstrated that AI-enabled devices can be targeted through adversarial manipulation of the underlying algorithms – not only through conventional network intrusion – and proposed a pre-market risk analysis framework extending security assessment to the behaviour of AI decision components [10]. Supply chain attacks, in which adversaries compromise a software vendor to gain simultaneous access to multiple downstream organisations, have been documented in healthcare IT. Argaw et al. identify insecure third-party interfaces as a primary structural vulnerability in hospital cybersecurity architectures [5,11].

Electronic health record security

Electronic health records are simultaneously the most operationally critical component of modern clinical workflow and among the most valuable tar-

gets for attackers. Health record data commands higher prices on illicit markets than financial data because a complete health record combines personal identifiers, diagnoses, medications, insurance information, and financial details that can be used for identity fraud, extortion, and fraudulent claims [1,4]. This economic reality drives targeted attacks specifically designed to exfiltrate health record data rather than encrypt it for ransom.

A quantitative study using structural equation modelling combined with artificial neural network analysis found that perceived cybersecurity risk is significantly associated with reduced trust in electronic health record systems and lower perceived performance among healthcare professionals [12]. These findings suggest that cybersecurity concerns may influence clinician engagement with digital health systems. Similarly, Arafa et al. report that perceived security plays an important role in shaping clinician acceptance and trust in emerging digital health technologies [1].

Core EHR security principles with direct relevance to clinical practice include: strong, unique credentials for each system supported by a password manager; multi-factor authentication (MFA) activated wherever available; minimum necessary access – each user accesses only data required for their current role; encryption of data in transit and at rest; and prompt reporting of anomalous system behaviour. Sharing login credentials with colleagues, even temporarily and in cases of clinical urgency, eliminates both technical access control and the audit trail that enables detection of unauthorised access.

The clinician's role in cybersecurity

Sociotechnical analyses consistently identify the human element as both the most frequent point of failure and the most important defensive resource in healthcare cybersecurity. Ewoh et al., in a 2025 scoping review published in the *Journal of Medical Internet Research*, propose a sociotechnical framework that integrates people, processes, and technology, placing clinicians at the centre of the security system rather than at its periphery [6]. The 2024 BMC qualitative study identified inadequate staff training and limited security awareness as key organisational risk factors, alongside broader systemic and governance-related challenges [13].

In day-to-day practice, clinicians make a continuous series of decisions with cybersecurity implications: whether to open an email attachment, use shared credentials for convenience, report a system anomaly, access patient data on a personal device.

Embedding security awareness into routine clinical behaviour – treating it as an element of professional competence alongside medication verification and infection control – is the most impactful intervention available at the individual level [5]. Prompt incident reporting is especially critical: unusual computer behaviour, unexpected system restarts, changes to the EHR interface appearance, unsolicited credential requests, and anomalous device behaviour can all indicate an active attack [5,7]. Alanazi's survey data show that a significant proportion of clinicians did not know where to direct a security report and doubted their report would receive a serious institutional response – a cultural failure with direct security consequences [5].

Advanced defensive technologies

AI-driven security systems can continuously monitor hospital networks, identify behavioural anomalies indicative of compromise, and isolate affected systems at speeds that manual oversight cannot match. The domain-specific machine-learning approaches demonstrated by ElSayed et al. and Mohammedi et al. illustrate how AI tools tailored to IoMT environments can address threat categories that generic security software fails to cover [8,9].

Blockchain technology has been proposed as a mechanism for ensuring the integrity and auditability of health records. The *Cluster Computing* systematic review identifies blockchain-based systems as among the most promising structural solutions for maintaining tamper-evident records of data access and modification – a property of particular value in environments where record authenticity is both a clinical and legal requirement [4]. Federated learning – a paradigm in which AI models are trained collaboratively across multiple institutions without patient data leaving each site – offers a path to more capable diagnostic algorithms while substantially reducing the security and privacy risks of centralised data aggregation [14].

The Zero Trust security model, endorsed by the World Economic Forum as a guiding architecture for healthcare cybersecurity, replaces the assumption that everything within a hospital network perimeter is trustworthy with continuous authentication and authorisation for every resource access event [15]. Ewoh et al. note that successful Zero Trust implementation requires alignment of technology, processes, and organisational culture – technical deployment alone is insufficient [6]. Regulatory frameworks such as GDPR in Europe and HIPAA/HITECH in the United States establish baseline requirements for data

protection and mandate breach notification obligations, with non-compliance potentially resulting in significant penalties. Healthcare cybersecurity bulletins from the U.S. HC3 highlight the relevance of these regulatory requirements amid ongoing cyber threats affecting the health sector [16].

Practical recommendations

For individual clinicians, credential management is the most immediately actionable area of responsibility. Strong, unique passwords for each system, with MFA enabled on every platform that supports it, are foundational; credentials must never be shared, and institutions should provide alternative emergency access protocols to avoid trading security for clinical urgency [2].

Alanazi reports variability in clinicians' awareness of cybersecurity threats and highlights uncertainty regarding institutional procedures for identifying and reporting suspicious communications, including potential phishing attempts [5].

Device-level security practices are widely recognised as important for reducing vulnerabilities in healthcare environments, particularly given the increasing attack surface associated with connected medical and information systems. From a user interaction perspective, perceived cybersecurity risks have also been shown to influence how healthcare professionals engage with electronic health record systems, highlighting the importance of secure system design and safe usage practices [7,12].

Studies highlight significant gaps in clinicians' cybersecurity awareness and uncertainty about institutional responsibilities, indicating the need for improved and context-sensitive cybersecurity education within healthcare environments. Both organisational and human-factor considerations are emphasised as important components of effective healthcare cybersecurity strategies [5,13]. Generic IT security content has limited impact; training using clinical scenarios – recognising a phishing message formatted as a laboratory result notification, understanding why credential sharing undermines both security and accountability – might produce greater and more durable behaviour change.

Technical measures should include network segmentation separating medical devices from administrative systems, regular vulnerability assessments, endpoint detection and response (EDR) deployment, and rigorously tested backup and recovery plans. IoMT devices warrant a dedicated institutional programme: central device inventories, network traffic monitoring, patch management where feasible, and

isolation of legacy devices that cannot be updated. Incident response plans must be documented, rehearsed with clinical leadership participation, and subject to systematic post-incident review.

Patient safety implications

The ultimate purpose of healthcare cybersecurity is to protect patients. Attacks that compromise data availability, disrupt device function, or immobilise clinical systems have direct consequences for diagnosis, treatment, and patient safety. Inaccessibility of allergy status, dosing errors attributable to device manipulation, and inability to order urgent investigations during system outages are documented outcomes of real-world ransomware attacks. Patient trust may also be eroded over the longer term. Data breaches have been associated in the literature with reduced patient confidence in healthcare systems, which may negatively influence openness in clinical communication.

Mitra et al. use a systems-theoretic framework to demonstrate that adversarial manipulation of machine learning models embedded in medical devices can lead to unsafe or erroneous outputs, highlighting limitations in conventional monitoring approaches for detecting such failures. These findings underscore the importance of robust safety and governance mechanisms for AI-enabled clinical decision support systems [10]. Along with these new possibilities, such systems also introduce new risks. Systems and models trained on single-centre datasets absorb and reproduce diagnostic habits and blind spots embedded in the environment. Such models can perpetuate single-institution biases when applied elsewhere [17].

Conclusion

Artificial intelligence offers transformative potential across many domains of clinical practice, from embryo selection in reproductive medicine to threat detection in cybersecurity, however, no technology is sufficient without the informed, vigilant clinician participation. The current threat environment continues to evolve: ransomware campaigns grow more sophisticated, Internet of Medical Things devices present novel attack surfaces, artificial intelligence is being weaponised, and supply chain compromises can affect entire regional health networks simultaneously. Advanced defensive technologies such as artificial intelligence-driven threat detection, blockchain integrity, federated learning and Zero Trust architecture are available and effective, but require strategic institutional commitment and adequate resources. Individual clinician behaviour remains indispensable

and cannot be substituted by technology: strong credential hygiene, vigilance against phishing, prompt incident reporting, and critical oversight of connected devices are professional responsibilities that belong

alongside medication safety and infection control in the daily practice of every clinician. The core message is straightforward: cybersecurity is a dimension of patient safety. It begins at the login screen.

References

1. Arafa A, Sheerah HA, Alsalamah S. Emerging digital technologies in healthcare with a spotlight on cybersecurity: a narrative review. *Information*. 2023;14(12):640.
2. Healthcare Information and Management Systems Society. 2024 HIMSS healthcare cybersecurity survey report [Internet]. Chicago: HIMSS; 2025 [cited 2026 May 15]. Available from: <https://cdn.sanity.io/files/sqo8bpt9/production/4f1c1968050411b8bf9335a187301881f9153b9f.pdf>
3. Ponemon Institute. Cyber insecurity in healthcare: the cost and impact on patient safety and care 2025 [Internet]. Sunnyvale (CA): Proofpoint; 2025 [cited 2026 May 15]. Available from: <https://www.proofpoint.com/sites/default/files/threat-reports/pfpt-us-tr-cyber-insecurity-healthcare-ponemon-report.pdf>
4. Nemec Zlatolas L, Welzer T, Lhotska L. Data breaches in healthcare: security mechanisms for attack mitigation. *Cluster Comput*. 2024;27(7):8639-54.
5. Alanazi AT. Clinicians' perspectives on healthcare cybersecurity and cyber threats. *Cureus*. 2023;15(10):e47026.
6. Ewoh P, Vartiainen T, Mantere T. Sociotechnical cybersecurity framework for securing health care from vulnerabilities and cyberattacks: scoping review. *J Med Internet Res*. 2025;27:e75584.
7. Deb S, Lupu E, Drakakis EM, Bharath AA, Leung ZK, Ma GR, et al. Securing the Internet of Medical Things (IoMT): real-world attack taxonomy and practical security measures [Internet]. 2025 [cited 2026 May 15]. Available from: <https://arxiv.org/pdf/2507.19609>
8. ElSayed Z, Abdelgawad A, Elsayed N. CryptoDNA: a machine learning paradigm for DDoS detection in healthcare IoT, inspired by crypto jacking prevention models [Internet]. 2025 [cited 2026 May 15]. Available from: <https://arxiv.org/pdf/2501.18549>
9. Mohamadi A, Ghahramani H, Asghari SA, Aminian M. Securing healthcare with deep learning: a CNN-based model for medical IoT threat detection. In: 19th Iranian Conference on Rad je primljen 2. VI 2026. Recenziran 19. VI 2026. Prihvaćen za štampu 24. VI 2026. BIBLID.0025-8105:(2026):LXXIX:7-8:215-219.
- Intelligent Systems (ICIS); 2024 Oct 23-24; Sirjan, Iran. Sirjan: Sirjan University of Technology, 2024. p. 168-73.
10. Mitra G, Hallajiyani M, Kim I, Dharmalingam AP, Elnawawy M, Iqbal S, et al. Systems-theoretic and data-driven security analysis in ML-enabled medical devices [Internet]. 2025 [cited 2026 May 15]. Available from: <https://arxiv.org/pdf/2506.15028>
11. Argaw ST, Troncoso-Pastoriza JR, Lacey D, Florin MV, Calcavecchia F, Anderson D, et al. Cybersecurity of hospitals: challenges and risk mitigation. *BMC Med Inform Decis Mak*. 2020;20:146.
12. Ala'a M, Ramayah T, Al-Sharafi MA. Exploring the impact of cybersecurity on using electronic health records and their performance among healthcare professionals: a multi-analytical SEM-ANN approach. *Technol Soc*. 2024;77:102592.
13. Burke W, Stranieri A, Oseni T, Gondal I. The need for cybersecurity self-evaluation in healthcare. *BMC Med Inform Decis Mak*. 2024;24(1):133.
14. Rieke N, Hancox J, Li W, Milletari F, Roth HR, Albarqouni S, et al. The future of digital health with federated learning. *NPJ Digit Med*. 2020;3:119.
15. World Economic Forum. A rise in healthcare cyberattacks calls for zero trust [Internet]. Geneva: World Economic Forum; 2023 [cited 2026 May 15]. Available from: <https://www.weforum.org/stories/2023/05/cyber-attacks-on-healthcare-rise-zero-trust/>
16. U.S. Department of Health and Human Services, Health Sector Cybersecurity Coordination Center. HC3 Healthcare: Cybersecurity Bulletin [Internet]. 2023 [cited 2026 May 15]. Available from: <https://www.hhs.gov/sites/default/files/hc3-healthcare-cybersecurity-bulletin-q1-2023.pdf>
17. Fogt F. The illusion of diagnostic agreement - institutional bias as a hidden force in modern medicine. *Med Pregl*. 2025;78(5-8):127-31.

CORRECTED VERSION ISPRAVLJENA VERZIJA

This is the corrected version of the article originally published in *Medicinski preglad/Medical Review*, 2026;79(3-6):143-146, republished in full to correct errors in the original. The authors and editors apologise for any inconvenience caused.

Čomić N, Puškar N, Radumilo D, Ivić S. The state of dental arch supporting zones in children in Vojvodina. *Med Pregl*. 2026;79(3-6):143-6.

THE STATE OF DENTAL ARCH SUPPORTING ZONES IN CHILDREN IN VOJVODINA

STANJE POTPORNIH ZONA ZUBNIH LUKOVA KOD DECE U VOJVODINI

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Corrected version
Ispravljena verzija
UDK 616.314-007-053.2(497.113)
<https://doi.org/10.2298/MPNS2608221E>

Abstract

Introduction. The supporting zone is an orthodontic term that defines the space from the distoproximal surface of the lateral permanent incisor to the mesial surface of the first permanent molar. During the period of deciduous and mixed dentition, this space consists of the deciduous canine, first and second deciduous molars, and primate diastemas, which are later replaced by the permanent canine and first and second premolars. The aim of this study was to determine the space available within the supporting zones to accommodate the permanent successor teeth in children from Vojvodina aged 9-11 years, and to assess whether the conditions for the second phase of tooth replacement were present. **Material and Methods.** Study models from patients of the Department of Orthodontics, Clinic of Dental Medicine of Vojvodina, were used. A total of 42 models from patients aged 9-11 years, with equal representation of both sexes, were analysed. Using OnyxCephTM software and the Moyers analysis, the required space within the supporting zones, the available space, and any differences between these values were calculated. The resulting values were compared according to sex, age and jaw quadrant. **Results.** The supporting zone showed sufficient space in 64.3% of cases in the maxilla, and in 54.8% in the mandible. In the remaining 35.7% of maxillary cases and 45.2% of mandibular cases, insufficient space was observed. No statistically significant difference (at the 0.05 level) was found according to sex, age or side of the jaw, whereas a significant difference was found between the maxilla and the mandible. **Conclusion.** The condition of the supporting zones in children in Vojvodina is satisfactory, as are the level and trend of continuous dental care.

Key words: Dental Arch; Child; Dentition, Mixed; Malocclusion; Orthodontics; Dental Care

Sažetak

Uvod. Potporna zona je ortodontski termin koji označava prostor od distoproskimalne površine stalnog bočnog sekutića do mezijalne površine prvog stalnog kutnjaka. Tokom perioda mlečne i mešovite denticije ovaj prostor čine mlečni očnjak, prvi i drugi mlečni kutnjak, kao i primatne dijasteme, a kasnije ih zamenjuju dva prekutnjaka i stalni očnjak. Potporna zona je ključna za smeštaj stalnih zuba tokom druge faze smene, njen integritet zavisi od očuvanosti mlečne denticije i rezervnog prostora. Cilj rada bio je da se ispita raspoloživi prostor u potpornim zonama kod dece uzrasta 9–11 godina u Vojvodini i procene uslovi za pravilno nicanje stalnih zuba. **Materijal i metode.** Analizirana su 42 studijska modela dece oba pola (9, 10 i 11 godina) sa Klinike za stomatologiju Vojvodine. Mojerševom analizom, uz pomoć programa OnyxCephTM, određeni su potreban i raspoloživ prostor u potpornim zonama. Rezultati su poređani prema polu, uzrastu i kvadrantu vilica, uz primenu t-testa. **Rezultati.** Dovoljan prostor u maksili utvrđen je u 64,3%, a u mandibuli u 54,8% slučajeva. Nedostatak prostora zabeležen je u 35,7% u maksili i 45,2% u mandibuli. Nije utvrđena statistički značajna razlika u odnosu na pol, uzrast i stranu vilice ($p > 0,05$), dok razlika između maksile i mandibule jeste značajna. **Zaključak.** Stanje potpornih zona kod dece u Vojvodini je zadovoljavajuće, ali se češće uočava nedostatak prostora u mandibuli, što ukazuje na značaj rane dijagnostike i preventivnih mera.

Ključne reči: zubni luk; dete; mešovita denticija; malokluzija; ortodoncija; stomatološka zdravstvena zaštita

Acknowledgement

The results presented in this paper are obtained in the framework of the project "Development and Application of Digital 3D Methods for the Fabrication of Dental Appliances", financed by

the Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina. (Project number: 0038856804 2025 09418 003 000 000 001)

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Introduction

The supporting zone is an orthodontic term that defines the space from the distoproximal surface of the lateral permanent incisor to the mesioproximal surface of the first permanent molar. During the period of deciduous and mixed dentition, this space consists of the deciduous canine, first and second deciduous molars, and diastemas [1]. The most stable diastemas are located between the lateral incisor and canine in the maxilla and between the canine and first molar in the mandible. These diastemas are referred to as primate or anthropoid spaces [2].

The width of deciduous molars together with canines and diastemas is greater than the width of their permanent successors, and this additional space is referred to as the leeway space. The leeway space amounts to 1.5 mm in the maxilla and 2.5 mm in the mandible. Its importance lies in accommodating the permanent canine and the first and second premolars, and in permitting the mesial movement of the lower molars to achieve an Angle Class I molar relationship and proper intercuspation (the mesial shift) [1,2]. An exception occurs in subjects with a Class III malocclusion, in whom the summed crown width of the mandibular incisors is greater than the average values in the general population [3].

Deciduous teeth form a functional unit that plays multiple roles until replaced by permanent teeth. They participate in all orofacial functions (breathing, swallowing, mastication, and speech), enable normal jaw growth and development, preserve space for successors, and contribute to facial aesthetics [4,5].

Premature tooth loss or reduced tooth width because of untreated approximal caries can disturb this balance, leading to reduction of the supporting zone, loss of arch length, and development of malocclusions [2,6,7]. Premature tooth loss is defined as loss of a deciduous tooth without eruption of its successor within six months, or when the root of the permanent successor has not developed at least two-thirds, as seen on radiographs [4,8].

Caries and its complications remain the most common aetiological cause of premature tooth loss. Dental trauma, most frequent between ages seven and ten, is another important factor [2].

The rate and degree of space loss depend on patient age, the lost tooth, and available space in the arch. A longer time interval between tooth loss and expected exfoliation leads to greater space loss [2]. The greatest and fastest space loss occurs after extraction of the second deciduous molar, especially in the mandible, and of the maxillary canine, owing to their late replacement. Individuals with primary crowding experience

more rapid space loss, while those with spaced dentition usually do not develop crowding or malocclusion [4].

To determine whether the available space is sufficient for permanent canines and premolars, Moyers analysis is used [5]. By summing the mesiodistal widths of the lower four permanent incisors and using Moyers tables, the predicted sizes of teeth in the supporting zone can be determined and compared with arch length. The results may indicate excess space, normal conditions, or lack of space [7,10,12]. Clinically, identifying space deficiency is most important, as it leads to secondary crowding and functional and hygienic complications [13,14].

The aim of this study was to determine the available space in supporting zones for the accommodation of permanent successor teeth in children from Vojvodina aged 9, 10 and 11 years, and to evaluate differences according to sex, age, and jaw quadrant.

Material and Methods

The study was conducted in January 2025 at the Clinic of Dental Medicine of Vojvodina, Faculty of Medicine, University of Novi Sad, with approval from the Ethics Committee. It was designed as a cross-sectional study using models from the Department of Orthodontics.

A total of 42 patient models were analysed (14 per age group), equally distributed between the sexes (21 male, 21 female), born between 1 January 2006 and 31 December 2009.

Using OnyxCeph™ software, the mesiodistal widths of the lower permanent incisors were measured and summed. The boundaries of the supporting zone were defined as the most prominent distal point of the lateral incisor and the mesial point of the first permanent molar.

Moyers analysis was used to calculate required space, available space, and differences for each patient. Results were compared by sex, age, and jaw quadrant. Statistical analysis was performed using the t-test, with results presented in tables and graphs.

Results

Measurement of supporting zones in 42 patients showed that in the maxilla, 27 children (64.3%) had sufficient space, while 15 (35.7%) did not.

In the mandible, 23 children (54.8%) had sufficient space, while 19 (45.2%) did not.

Further analyses showed: No statistically significant differences based on age, sex, or side of the jaw; Statistically significant differences between maxilla and

Table 1. T-test values comparing the required and actual values of the supporting zone

Age	Sex	Maxilla		Mandible	
		left	right	left	right
9 years	Female	0.05	0.54	0.16	0.54
	Male	0.93	0.45	0.59	0.44
10 years	Female	0.11	0.88	0.79	0.44
	Male	0.31	0.64	0.33	0.83
11 years	Female	0.87	0.44	0.61	0.19
	Male	0.30	0.13	0.50	0.63

*Greyed out cells mark significant p-values (≤ 0.05) from t-test comparison

Table 2. Mean difference between required and available space in the supporting zones, expressed in millimetres

Age	9 years [mm]	10 years [mm]	
Maxilla	0.586	1.229	1.179
Mandible	1.143	-0.293	-0.243

Table 3. T-test values comparing free-space differences according to the child's age

Age	9 and 10 years	9 and 11 years	
Maxilla	0.66	0.66	0.97
Mandible	0.52	0.41	0.98

Table 4. T-test values comparing free-space differences between male and female participants

Age	9 years	10 years	
Maxilla	0.25	0.78	0.64
Mandible	0.46	0.51	0.90

Table 5. T-test values comparing free-space differences according to side of the jaw

Age	10 years				11 years	
	female	male	female	male	female	male
Mandible	0.15	0.09	0.20	0.26	0.20	0.40
Maxilla	0.12	0.07	0.20	0.27	0.10	0.06

Table 6. T-test values comparing free-space differences according to jaw

Age	9 years		10 years		11 years	
	female	male	female	male	female	male
Left	0.42	0.31	0.07	0.45	0.38	0.32
Right	0.49	0.03	0.25	0.47	0.03	0.10

mandible in certain subgroups; 9-year-olds had sufficient space in both jaws, while 10- and 11-year-olds showed space deficiency in the mandible (**Tables 1-6**).

Discussion

The present study showed a higher percentage of sufficient space for adequate progression of the second phase of tooth replacement (64.3% in the maxilla and 54.8% in the mandible sufficient vs 35.7% in the maxilla and 45.2% in the mandible insufficient). If dental caries and premature tooth loss are regarded as the

main aetiological factors in reducing the required space within the supporting zones, the results are partly consistent with the study by Tadić et al. (2015) on the prevalence of caries among patients referred for orthodontic examination. They reported a prevalence of caries in deciduous teeth of 68% in mixed dentition. The prevalence of caries in permanent teeth was 21% in mixed dentition and 40% in permanent dentition [15]. These findings are discouraging, as studies conducted in Croatia in 1980, 1984, and 1990 demonstrated a positive trend towards reduced caries prevalence. Miličić et al. reported a caries prevalence

of 80.3% in 1980 and, only 4 years later, a decrease in untreated caries prevalence to 40.7% [16,17]. In a 1990 study, Visković et al. reported untreated carious lesions in 20.3% of the examined sample [7].

Tooth and dental arch dimensions vary among populations, so selecting an appropriate analysis is important to obtain relevant results. The present study used Moyers analysis. Although a study conducted in Nepal did not support the use of Moyers tabulated values, studies conducted in countries geographically closer to ours, such as Italy and Croatia, emphasise the considerable importance of Moyers analysis [10,11,14,18,19]. The study by Umićević-Davidović et al. supports the clinical applicability of Moyers analysis, with additional caution in female patients, consistent with our results obtained by comparing tabulated/required and measured/actual values [12]. The results showed a statistically significant difference in the left maxilla among 9-year-old female participants, whereas the other study groups showed no statistically significant differences. This may also reflect the level of dental health care and patients' motivation to maintain oral hygiene and attend regular dental visits [20].

At the chosen significance level, comparison of free-space differences between children aged 9 and 10, 9 and 11, and 10 and 11 years showed no statistically significant differences. This may be explained by the trend of continuous dental care and health education of children in preschool institutions, with continuation of such education in schools [21,22]. Banu et al. investigated the DMFT (decayed, missing, filled teeth) index in children aged 8-9 and 10-11 years and found that the latter group had a higher DMFT index, which is not consistent with our results [23].

When we compared the differences between required and measured supporting-zone dimensions between male and female participants, we observed a higher percentage of sufficient available space in the maxilla among 9-year-old females and 11-year-old males, whereas 10-year-olds showed equal percentage distributions. In the mandible, only 10-year-olds differed, with more male participants having sufficient

space. t-test analysis showed no statistically significant difference irrespective of patient age or the jaw analysed. Tadić et al. reported more healthy and restored deciduous teeth in the male population and somewhat more active caries in deciduous teeth in the female population, but no statistically significant difference, consistent with the present study [15]. Similarly, a study conducted in Romania reported a higher prevalence of caries among females without a statistically significant difference, although the DMFT index was significantly higher in the female population [23]. Several authors have concluded that the crown diameters of teeth occupying the supporting zone are greater in males than in females and may therefore produce misleading results regarding the possibility of accommodating permanent teeth during the second phase of tooth replacement; our study does not support these findings [11,12,14,24].

Statistical analysis of the mesiodistal widths of teeth within the supporting zone showed no significant difference between the left and right sides [12-14,25]. This finding, together with our results, indicates no preferential use of either side during oral hygiene and mastication [26].

Comparison of free-space differences between the jaws revealed a statistically significant difference on the right side in 9-year-old male and 11-year-old female participants. This is supported by Visković et al., who reported a higher percentage of intact teeth in the maxilla than in the mandible. In contrast, the mandible had more restored teeth because mandibular teeth have greater caries involvement [7]. This is inconsistent with the fact that mandibular teeth benefit more from self-cleansing by saliva and that self-cleansing improves with larger diastemas during tooth replacement [1,27].

Conclusion

The condition of supporting zones of dental arches in children in Vojvodina is satisfactory, reflecting an adequate level and trend of continuous dental care.

References

1. Nakaš E, Tiro A, Džemidžić V, Redžebagić-Vražalica L, Ajanović M. Osnovi ortodontske dijagnostike. Sarajevo: Stomatološki fakultet sa klinikama; 2014.
2. Matošević D. Etiologija i terapija preranog gubitka mlječnih zubi. Sonda. 2003;8-9(2):108-13.
3. Puškar N, Puškar M, Vučinić P, Ivić S, Petrović Đ. Determination of dentoalveolar parameters in patients with progenia. Med Pregl. 2022;75(9-10):279-83.
4. Tanić T, Blažej Z, Radojičić J. Posledice prevremenog gubitka mlečnih bočnih zuba. Facta Universitatis Series: Medicine and Biology. 2008;15(2):68-73.
5. Marković M, editor. Ortodoncija. 3rd ed. Beograd-Zagreb: Medicinska knjiga; 1989.
6. Stanić O, Anđelković A, Mirnić J, Predin T. Prevremeni gubitak mlečnih zuba. Medicina danas. 2013;7(1-3):11-5.
7. Visković R, Vujanović M, Brčić V. Prevalencija ortodontskih anomalija te analiza i procjena dentalnog zdravlja djece predškolske dobi unutar triju grupacija u Zadru. Acta Stomatol Croat. 1990;24(4):271-80.
8. Marić D, Vukić-Čulafić B. Praktikum iz ortodoncije: osnove praktične nastave. 2nd ed. Novi Sad: Medicinski fakultet Novi Sad; 1998.

9. Jović M, Mirnić J, Predin T, Anđelković A. Uloga i značaj držača prostora kao interceptivne stomatološke metode. *Medicina danas*. 2012;11(10-12):330-3.

10. Lapter V, Slivjanovski D. Ortodontska vrijednost procjene meziodistalnih dimenzija definirane skupine zuba. *Acta Stomatol Croat*. 1974;8(1):23-7.

11. Lapter V, Slivjanovski D. Dopunska analiza meziodistalnih dimenzija očnjaka i pretkutnjaka. *Acta Stomatol Croat*. 1975;9(3):113-8.

12. Umičević-Davidović M, Arbutina A, Arapović-Savić M, Marin S. Procena veličine neizniklih stalnih očnjaka i premolara u mešovitoj denticiji. *Glasnik Antropološkog društva Srbije*. 2012;47:17-25.

13. Khanna R, Pandey RK, Tripathi S. Effect of intermaxillary tooth-size discrepancy on accuracy of prediction equations for mixed dentition space analysis. *Eur Arch Paediatr Dent*. 2015;16(2):211-7.

14. Cirulli N, Ballini A, Cantore S, Farronato D, Inchingolo F, Dipalma G, et al. Mixed dentition space analysis of a Southern Italian population: new regression equations for unerupted teeth. *J Biol Regul Homeost Agents*. 2015;29(2):515-20.

15. Tadić K, Katić V, Špalj S. Učestalost karijesa u pacijenata upućenih na ortodontski pregled. *Acta Stomatol Croat*. 2018;52(2):123-31.

16. Miličić A, Gaži-Čoklica V. Razvojne karakteristike kasne mliječne i rane mješovite denticije u prevenciji ortodontskih anomalija. *Acta Stomatol Croat*. 1980;14(3-4):72-80.

17. Miličić A, Gaži-Čoklica V, Hunski M. Analiza incidenције ortodontskih anomalija i karijesa mliječnih zubi kod zagrebačke djece. *Acta Stomatol Croat*. 1984;18(2):95-103.

Rad je primljen 2. IV 2026.

Recenziran 7. V 2026.

Prihvaćen za štampu 14. V 2026.

BIBLID.0025-8105:(2026):LXXIX:7-8:221-225.

18. Giri J, Pokharel PR, Gyawali R, Timsina J, Pokhrel K. New regression equations for mixed dentition space analysis in Nepalese mongoloids. *BMC Oral Health*. 2018;18(1):214.

19. Muretić Ž. Važnost preventivskih mjera u ortodonciji. *Acta Stomatol Croat*. 1996;30(2):137-40.

20. Ljaljević A, Matijević S, Terzić N, Andjelić J, Mugoša B. Značaj održavanja oralne higijene za zdravlje usta i zuba. *Vojnosanit Pregl*. 2012;69(1):16-21.

21. Vučemilović Lj. Zdravstveni odgoj u vrtiću. Dijete vrtić obitelj. 2013;(72):30-1.

22. Rajić Z, Valentak Lj, Jukić J. Opravdanost primjene preventivnih mjera u radu sa školskom djecom od 6 do 14 godina. *Acta Stomatol Croat*. 1995;29(3):159-66.

23. Banu A, Serban C, Pricop M, Urechescu H, Vlaicu B. Dental health between self-perception, clinical evaluation and body image dissatisfaction - a cross-sectional study in mixed dentition pre- pubertal children. *BMC Oral Health*. 2018;18(1):74.

24. Altherr ER, Koroluk LD, Phillips C. Influence of sex and ethnic tooth-size differences on mixed-dentition space analysis. *Am J Orthod Dentofacial Orthop*. 2007;132(3):332-9.

25. Mishra RK, Devagiri V. Comparison and testing the reliability of two non-radiographic techniques of mixed dentition space analysis in Nepalese population. *Journal of College of Medical Sciences-Nepal*. 2017;13(4):410-5.

26. Romić Knežević M, Knežević I, Gabrić Pandurić D. Temporomandibularni poremećaji. *Sonda*. 2012;13(23):27-31.

27. Šurdilović D, Stojanović I, Apostolović M, Igić M, Kostadinović Lj, Trčković Janjić O. Značaj fosfatnog pufera pljuvačke u evaluaciji učestalosti karijesa kod dece. *Acta stomatologica Naissi*. 2009;25(59):851-8.

REPORTS FROM THE DLV BRANCHES *IZVEŠTAJI IZ PODRUŽNICA DLV*

GENERAL HOSPITAL VRBAS – REPORT ON THE INTRODUCTION OF PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG) PLACEMENT

IZVEŠTAJ O ZAPOČINJANJU PLASIRANJA PERKUTANE ENDOSKOPSKE GASTROSTOME (PEG) U OPŠTOJ BOLNICI VRBAS

At General Hospital Vrbas, percutaneous endoscopic gastrostomy (PEG) placement has been introduced to improve nutritional support and provide long-term enteral feeding for patients with preserved gastrointestinal function who are unable to maintain adequate oral intake.

PEG is a minimally invasive procedure that provides direct access to the stomach through the abdominal wall under endoscopic guidance, allowing safe and effective long-term administration of enteral nutrition, medications, and nutritional therapy.

Compared with long-term nasogastric feeding, PEG offers several advantages, including improved patient comfort and tolerance, reduced risk of accidental tube removal, easier administration of nutrition, and better suitability for prolonged nutritional support. It preserves the physiological use of the gastrointestinal tract and is particularly valuable in critically ill patients, neurological patients, and those with swallowing impairment.

To date, five PEG tubes have been successfully placed. All procedures were completed uneventfully, without any recorded complications. Two of five patients were discharged home following post-procedural monitoring.

The introduction of PEG placement enables more advanced management of patients requiring prolonged enteral nutrition, including those recovering from cerebrovascular events, those with neurological disorders, prolonged disorders of consciousness after resuscitation, and other conditions associated with dysphagia and inadequate oral intake.

The procedures were performed using a multidisciplinary approach, following careful assessment of indications, appropriate patient preparation, and standard safety measures. All PEG placements performed so far were completed successfully, without immediate procedure-related complications. Standard post-procedural monitoring and gastrostomy care were provided.

The introduction of this procedure represents an important improvement in healthcare quality at General Hospital Vrbas, contributing to the development of modern nutritional support, reducing the need for

U Opštoj bolnici Vrbas započeto je izvođenje procedure plasiranja perkutane endoskopske gastrostome (PEG) u cilju unapređenja nutritivne podrške i obezbeđivanja mogućnosti dugotrajnog enteralnog hranjenja kod bolesnika sa očuvanom funkcijom gastrointestinalnog trakta, ali sa nemogućnošću adekvatnog oralnog unosa hrane.

Perkutana endoskopska gastrostoma – PEG predstavlja minimalno invazivnu metodu kojom se, uz pomoć endoskopske kontrole, formira pristup želucu kroz prednji trbušni zid, čime se omogućava sigurna i dugotrajna primena enteralne ishrane, lekova i dodatne nutritivne terapije.

PEG ima značajne prednosti u odnosu na dugotrajno nazogastrično hranjenje jer omogućava bolju toleranciju kod pacijenata, veću udobnost, smanjenje rizika od slučajnog uklanjanja sonde, lakšu primenu ishrane i bolju mogućnost sprovođenja dugotrajne nutritivne potpore. Ova metoda omogućava očuvanje funkcije gastrointestinalnog trakta, što je od posebnog značaja kod kritično obolelih, neuroloških pacijenata i bolesnika sa poremećajem gutanja.

Uvođenjem PEG procedure omogućeno je savremenije i kvalitetnije zbrinjavanje bolesnika kojima je potrebna produžena enteralna ishrana, posebno kod stanja nakon cerebrovaskularnih inzulta, neuroloških oboljenja, postreanimacionih stanja sa produženim poremećajem svesti, kao i drugih stanja praćenih disfagijom i nemogućnošću adekvatnog oralnog unosa.

Do sada je plasirano pet PEG sondi. Sve procedure su protekle uredno, bez registrovanih komplikacija. Od pet bolesnika dva su nakon postproceduralnog nadzora otpuštena na kućno lečenje.

Procedure su realizovane uz multidisciplinarni pristup, uz prethodnu procenu indikacija, adekvatnu pripremu bolesnika i sprovođenje standardnih mera bezbednosti. Svi do sada izvedeni plasmani PEG-a protekli su uredno, bez neposrednih proceduralnih komplikacija. Nakon intervencije sproveden je standardni postproceduralni nadzor i nega gastrostome.

Uvođenje ove procedure predstavlja značajan korak u unapređenju kvaliteta zdravstvene zaštite u Opštoj bolnici Vrbas i doprinosi razvoju savremene nutritivne



Figure 1/Slika 1



Figure 2/Slika 2



Figure 3/Slika 3

Procedure performed/Slike izvođenja procedure

patient transfers to other institutions, and providing access to this important therapeutic option for patients in need.

potpore, smanjenju potrebe za transportom pacijenata u druge ustanove i omogućavanju dostupnosti ove metode bolesnicima kojima je ona potrebna.

*Dejan Zahorjanski, Nikola Japundžić, Milica Gojković
Opšta bolnica Vrbas*

ABSTRACTS - SkoNS 2026 - Second meeting of ASTAS and MAIM with international participation, Novi Sad, 27.02.-01.03.2026.

The abstracts published in this section were presented at the SkoNs 2026 meeting and were selected by the Scientific Committee for relevance and scientific merit. They have **not** undergone the Journal's peer-review process. The content, accuracy and opinions expressed are the sole responsibility of the authors and do not reflect the views of the Journal, its Editors or the Publisher.

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REZULTATI REOPERACIJA NESANIRANIH PRELOMA TELA NADLAKATNE KOSTI

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Sažetak

Uvod. Prelomi tela nadlaktatne kosti u oko 60% slučajeva se događaju kod populacije starije životne dobi, sa osteopenijom/osteoporozom, usled padova na ravnom. Prosečno vreme zarastanja iznosi 10 nedelja (od 6,5 do 22), sa stopom nesrastanja oko 7%. Nesrasle frakture zahtevne su za operativno lečenje zbog: kontraktura zglobova, lošeg kvaliteta kosti, slabog potencijala zarastanja, udruženih oboljenja i čistih lezija žbičnog živca – do 22% kod Holstejn-Luis (*Holstein-Lewis*) tipa preloma. Cilj studije predstavlja prikaz rezultata različitih operativnih metoda lečenja pseudoartroza dijafize humerusa. **Materijal i metode.** Retrospektivna studija je uključila 17 pacijenata prosečne starosti 59,5 godina, lečenih: intramedularnim klinom i zaključavajućim pločama sa zavrtnjima u po sedam slučajeva i tri spoljašnjim fiksatorima (SF) po Mitkoviću ili Ilizarovu. Studija analizira RTG snimke tri i šest meseci nakon reoperacije, prikazuje lečenje komplikacija i rezultate funkcionalnih testova (Constant za rame i Mayo skor za lakat). **Rezultati.** Nismo zabeležili značajnu razliku u funkcionalnim testovima među grupama lečenih klinom (71,3 tj. 81,0) i pločom (72,0 tj.

77,5), uz zadovoljavajuće rezultate spoljnjih fiksatora (63,7, tj. 62,5), iako su bili indikovani kod najtežih slučajeva (nakon otvorenih preloma). Među komplikacijama je bilo: osam uglavnom privremenih jatrogenih lezija žbičnog živca (sa spontanom opravkom u 85% slučajeva tokom prvih šest postoperativnih meseci), pet nezarastanja (29%) praćenih pucanjem implantata (tri ploče i dva klina) i dve duboke infekcije. **Zaključak.** Kod inficiranih pseudoartroza najbolje rezultate postizali smo primenom SF po Ilizarovu, kod neinficiranih: ekstrakcijom postojeće ploče, spongioplastikom i reosteosintezom pomoću LCP. Pseudoartroze nakon osteosinteze intramedularnim klinom lečili smo njegovom ekstrakcijom, rimovanjem i postavljanjem klina većeg dijametra. Zaključavajući klinovi doprineli su najboljim funkcionalnim rezultatima, a otvorena repozicija je češće uzrokovala jatrogena oštećenja *n. radialis*. I pored reoperacija kod 29% starijih pacijenata nije došlo do zarastanja te su perzistirale kontrakture lakta i ramena. Izbor implantata i hirurškog pristupa treba da je individualan.

Ključne reči: prelomi nadlaktatne kosti; nesrasli prelomi; dijafiza; ponovna operacija; ishod lečenja

PORODIČNA POVEZANOST POVREDE PREDNJEG UKRŠTENOG LIGAMENTA

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Sažetak

Uvod. Povrede prednjeg ukrštenog ligamenta (ACL) su u stalnom porastu, sa prevalencijom u sportskoj populaciji i iziskuju višenedeljni oporavak. Cilj ovog istraživanja je da utvrdi povezanost javljanja povrede prednjeg ukrštenog ligamenta sa porodičnom predispozicijom za povrede prednjeg ukrštenog ligamenta. **Materijal i metode.** Istraživanje je retrospektivnog karaktera, gde je uključeno 1.065 pacijenta urasta do 29 godina života, muškog i ženskog pola. Svim ispitanicima je dijagnostikovana povreda ACL-a. Podaci o ispitanicima za ovu studiju su prikupljeni na Klinici za ortopedsku hirurgiju i traumatologiju Kliničkog centra Vojvodine u Novom Sadu. **Rezultati.** Pri statističkoj analizi podataka 1.065 pacijenata lečenih na Klinici za ortopediju i traumatologiju Kliničkog centra Vojvodine dobili smo sledeće rezultate. U našem istraživanju 78,6% ispitanika je bilo muškog pola, dok je 21,4% bilo ženskog pola. Koristeći χ^2 test za analizu statistički značajne razlike u javljanju povrede prednjeg ukrštenog ligamenta povezane sa porodičnom predispozicijom, u grupi profesionalnih sportista muškog pola i mlađih od 19 godina, dobili smo vrednost $\chi^2 = 115,14$ $p = 0,00$ ($p < 0,01$), u grupi rekreativnih sportista muškog pola i mlađih od 19 godina dobili

smo vrednost $\chi^2 = 56,64$ $p = 0,00$ ($p < 0,01$). Za grupu profesionalnih sportista muškog pola i mlađih od 29 godina dobili smo vrednost $\chi^2 = 135,04$ $p = 0,00$ ($p < 0,01$), a za grupu istog pola i uzrasta rekreativnih sportista vrednost $\chi^2 = 572,14$ $p = 0,00$ ($p < 0,01$). Pri analizi podataka ženskih ispitanica rezultati su sledeći. U grupi ispitanica ženskog pola, uzrasta do 19 godina i koje su se profesionalno bavile sportom vrednost χ^2 test je $\chi^2 = 64,72$ $p = 0,000$ ($p < 0,01$), u grupi uzrasta do 19 godina koje su se bavile rekreativno sportom $\chi^2 = 35,76$ $p = 0,000$ ($p < 0,01$). U grupi pacijentkinja starosti do 29 godina i profesionalnim bavljenjem sportom vrednosti su bile $\chi^2 = 39,72$ $p = 0,000$ ($p < 0,01$), a u grupi ispitanica koje su se rekreativno bavile sportom $\chi^2 = 20,51$ $p = 0,000$ ($p < 0,01$). **Zaključak.** Iz rezultata sprovedenog istraživanja, ne može se zaključiti da porodična povezanost utiče na učestalost povrede prednjeg ukrštenog ligamenta kod ispitanog uzorka. Uz ograničenje u generalizaciji rezultata na širu populaciju, pošto u sprovedenom istraživanju nije bilo moguće obuhvatiti ispitanike sa povredama drugih anatomskih struktura zgloba kolena.

Ključne reči: povrede prednjeg ukrštenog ligamenta; prednji ukršteni ligament; genetska predispozicija za bolesti; sport; sportisti

VREME POVREDE PREDNJEG UKRŠTENOG LIGAMENTA

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Sažetak

Uvod. Prednji ukršteni ligament (ACL) je glavni stabilizator i najčešće povređivani ligament zgloba kolena. Povrede LCA tipično nastaju tokom sportskih aktivnosti. S obzirom na učestalost javljanja i na činjenicu da najčešće zahvataju mladu, sportski i radno aktivnu populaciju, povrede ACL predstavljaju značajan epidemiološki problem. Cilj ovog rada je utvrditi u kom delu treninga, sezone, u kom mesecu, danu u nedelji i delu dana najčešće dolazi do povreda LCA kod profesionalnih i rekreativnih sportista. **Materijal i metode.** Istraživanje je obuhvatilo 1.152 pacijenata lečenih na Klinici za ortopedsku hirurgiju i traumatologiju Kliničkog centra u Novom Sadu od 2012. do 2017. godine. Od 1.152 ispitanika, 671 pacijent se bavi sportom rekreativno, a 481 profesionalno. **Rezultati.** Značajno više ispitanika povredilo je LCA na sredini treninga ($p < 0,001$). Rekreativni sportisti se najčešće povređuju na sredini sezone, dok se profesionalni sportisti najčešće povređuju na početku sezone.

Statistički više povreda se desilo na sredini sezone ($p < 0,001$). Najveći broj povreda kod rekreativnih sportista je zabeležen u maju, dok je kod profesionalnih sportista to slučaj sa oktobrom. Nedelja je dan sa najvećim brojem povreda kod rekreativnih sportista dok je kritičan dan za povredu profesionalnih sportista subota. Postoji statistički značajna razlika u korist povreda nastalih tokom subote ($p < 0,001$). Obe grupe sportista se najčešće povređuju posle podne. **Zaključak.** Najviše povreda LCA je zabeleženo na sredini treninga, tokom sredine sezone, u oktobru, subotom i u poslepodnevnim časovima. Protokoli za prevenciju povreda bi mogli da budu sledeći veliki korak u tretmanu povreda LCA. Saznanje kada povrede LCA najčešće nastaju bi moglo da dugoročne rezultate i redukuje broj i incidenciju povreda LCA.

Ključne reči: povrede prednjeg ukrštenog ligamenta; sportisti; sport; sportske povrede; vremenski faktori; faktori rizika; godišnja doba

ASYMPTOMATIC HYPERTHYROIDISM WITH COMORBID OSTEOPOROSIS AND HYPERTENSION IN A 55-YEAR-OLD WOMAN: CASE REPORT AND SUCCESSFUL MANAGEMENT

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UDK 616.12-008.331.1-085

UDK 616.71-007.234-085

UDK 616.441-008.61-085

Sažetak

Introduction. A 55-year-old patient presented to the outpatient clinic for hypertension grade 2 control and treatment (150-160/95 mmHg), managed with lisinopril 10 mg + hydrochlorothiazide 25 mg daily for 10 years and nebivolol 5 mg for 4 years. Asymptomatic subclinical hyperthyroidism was incidentally detected during routine evaluation. Duration of thyroid condition unknown. No family history of autoimmune diseases. In menopause for 4 years. **Clinical and Laboratory Findings.** BMI 26 kg/m², no tachycardia or tremor. BP 150/95 mmHg. Labs: TSH 0.12 mIU/L (0.4-4.0), fT4 24 pmol/L (12-22), fT3 7.5 pmol/L (3.1-6.8), anti-TPO antibodies positive (autoimmune aetiology). TSH after 6 weeks: 0.46 mIU/L. Thyroid ultrasound: heterogeneous echotexture, nodular changes, normal volume, mildly increased vascularity. DEXA scan: T-score -2.7 at lumbar spine (osteoporosis), calcium 2.15 mmol/L, vitamin D 18 ng/mL (deficient), calcitonin and PTH normal. ECG: sinus rhythm, rate 72/min, echocardiogram: normal left ventricle. **Treatment and**

Outcome. Per ESC/ESH 2024 guidelines, first-line for grade 2 hypertension is an ACEI + CCB combination (T. Ramipril/amlodipine 5/5 mg daily); nebivolol retained temporarily because of its beta-blockade effect on thyrotoxicosis. For hyperthyroidism: thiamazole 5 mg daily. For osteoporosis: bisphosphonate (alendronate 70 mg weekly) per IOF guidelines. After 7 months: TSH 2.1 mIU/L, fT4 normalised, DEXA T-score improved to -2.3. Nebivolol discontinued, BP 135/85 mmHg. Patient remains asymptomatic. **Conclusion.** Early detection during routine visits and targeted therapy yield excellent outcomes in asymptomatic hyperthyroidism with osteoporosis. Fracture risk is 4.5-fold higher in patients with low TSH and osteoporosis. Cardiovascular risk (stroke, MI, mortality) is elevated in patients with hypertension and hyperthyroidism; thus, regular monitoring of thyroid hormones, ultrasound, and DEXA is essential.

Key words: Hyperthyroidism; Osteoporosis; Hypertension; Treatment Outcome

HORMONSKA SUPSTITUCIJA KAO PREVENTIVNA STRATEGIJA U HIRURŠKOJ MENOPAUI

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UDK 618.173-085:615.357

Sažetak

Uvod. Hirurška menopauza predstavlja složen klinički entitet, povezan sa povećanim rizikom od metaboličkih i kardiovaskularnih poremećaja, kognitivnih deficita i smanjenja koštane gustine, što sve zajedno dovodi do značajnog narušavanja kvaliteta života. Cilj ove studije bio je da vizualizuje dinamiku parametara koštanog metabolizma tokom prve godine primene hormonske supstitucione terapije. **Materijal i metode.** Retrospektivna kohortna studija obuhvatila je 42 pacijentkinje sa Klinike za endokrinologiju, dijabetes i bolesti metabolizma u Novom Sadu, praćene u sklopu Ambulante za menopauzalna i klimakterična stanja, nakon hirurškog ili radijacionog tretmana ginekoloških karcinoma. Upoređeni su parametri mineralne koštane gustine na lumbalnoj kičmi (T-skor) i biomarkeri koštane remodelacije, uključujući P1NP i Crosslaps kod žena koje su koristile hormonsku supstitucionu terapiju (estrogenske ili kombinovane preparate) i kod onih bez terapije. **Rezultati.** Između grupa nije registrovana statistički značajna razlika u

pogledu T-skora ($p = 0,875$), vrednosti BMD ($p = 0,606$), P1NP ($p = 0,686$) i Crosslaps ($p = 0,865$). S obzirom na to da ipak postoji trend porasta vrednosti pomenutih parametara nakon hormonske supstitucije, statistička značajnost najverovatnije izostaje usled malog broja ispitanica i kratkotrajne izloženosti terapijskom protokolu. S obzirom na prosečnu starost od 44 godine, primarna ovarijalna insuficijencija je isključena, ali prerana menopauza je prisutna. **Zaključak.** Osteoporoza nije evidentirana ni u jednoj grupi ispitanica, međutim, povišene vrednosti P1NP, T-skora i mineralne koštane gustine, kao i diskretna poboljšanja u sintezi kolagena tipa 1 u grupi na hormonskoj supstitucionoj terapiji sugerišu protektivni efekat terapije na koštani metabolizam. Dobijeni podaci ističu važnost pravovremene i adekvatne terapijske intervencije u prevenciji osteoporoze kod žena u prevremenoj menopauzi.

Ključne reči: hormonska supstitucionna terapija; prevremena menopauza; menopauza; hirurške operative procedure; gustina kostiju

THE INFLUENCE OF MUSCLE STRENGTH ON QUALITY OF LIFE IN PATIENTS WITH SARCOPENIA

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Abstract

Introduction. According to the definition used in the literature, the prevalence of sarcopenia is 5-13% in people aged 60–70 years and 11-50% in those over 80 years. Sarcopenia is a progressive, generalised skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality. **Material and Methods.** This cross-sectional study included 75 patients over a period of 5 months. Most were nursing homes residents in the Republic of North Macedonia, aged 60 and over. Sarcopenia was diagnosed by assessing muscle mass (bioimpedance analysis), physical performance (gait speed), muscle strength (handgrip

strength), and a SARC-F score of 4 or higher. Patients diagnosed with sarcopenia completed the SF-36 questionnaire to assess quality of life. **Results.** Patients without sarcopenia had significantly higher muscle quality than those with sarcopenia ($p = 0.001$), higher muscle strength (handgrip strength; $Z = 3.27$, $p = 0.001$), and higher gait speed ($Z = -5.83$, $p < 0.001$). **Discussion and Conclusion.** Quality of life in patients with sarcopenia declined with increasing age. Muscle strength was the parameter most strongly associated with quality of life, and higher muscle quality was also associated with better quality of life.

Key words Sarcopenia; Muscle Strength; Quality of Life; Geriatric Assessment

IMPACT OF VITAMIN D AND NUTRITIONAL STATUS ON THE AMOUNT OF VISCERAL ADIPOSE TISSUE

EFEKAT VITAMINA D I NUTRITIVNOG STATUSA NA KOLIČINU VISCERALNOG MASNOG TKIVA

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UDK 616-008.9:[616.391:577.161.2]

Abstract

Introduction. The association between vitamin D concentration and body fat distribution has been widely investigated; however, the relationship between serum 25-hydroxyvitamin D and visceral adiposity in older adults remains unclear. This study aimed to examine the association among vitamin D levels, visceral adipose tissue, and nutritional status. **Material and Methods.** This retrospective study included 450 participants of both sexes aged 65–89 years. Serum 25(OH)D concentration was measured, nutritional status was assessed using the Mini Nutritional Assessment questionnaire, and visceral adipose tissue was quantified by dual-energy X-ray absorptiometry (DEXA). We performed correlation analysis and multiple linear regression. **Results.** No statistically significant association was found between serum vitamin D concentration and visceral adipose tissue ($p > 0.05$). The total Mini Nutritional Assessment score was not significantly correlated with visceral adiposity. In multivariate analysis, vitamin D was not identified as an independent predictor. Certain nutritional parameters, including body mass index and selected questionnaire components, were statistically significant. **Conclusion.** Serum vitamin D concentration was not associated with visceral adipose tissue in the elderly population studied. Specific nutritional indicators may help evaluate fat distribution.

Key words: Vitamin D; Nutritional Status; Adipose Tissue; Intra-Abdominal Fat; Body Composition; Aged

Sažetak

Uvod. Povezanost između koncentracije vitamina D i raspodele masnog tkiva predmet je brojnih istraživanja, ali odnos između serumskog 25-hidroksivitamina D i visceralne adipocitoze kod starijih osoba nije dovoljno razjašnjen. Cilj rada bio je ispitivanje povezanosti koncentracije vitamina D sa količinom visceralnog masnog tkiva i nutritivnim statusom. **Materijal i metode.** Retrospektivna studija obuhvatila je 450 ispitanika oba pola, uzrasta 65–89 godina, prosečne starosti od 73 godine. Kod svih ispitanika određena je koncentracija 25(OH)D u serumu – kalcidiola, procenjen nutritivni status primenom *Mini Nutritional Assessment* upitnika i izmerena količina visceralnog masnog tkiva metodom *dual-energy X-ray* apsorpcimetrije. Statistička analiza uključivala je korelacionu analizu i višestruku linearnu regresiju. **Rezultati.** Nije utvrđena statistički značajna povezanost između koncentracije vitamina D i količine visceralnog masnog tkiva ($p > 0,05$). Ukupan skor *Mini Nutritional Assessment* upitnika nije pokazao značajnu korelaciju sa visceralnom adipocitozom. U regresionom modelu koncentracija vitamina D nije identifikovana kao nezavisan prediktor količine visceralnog masnog tkiva. Pojedini nutritivni parametri, uključujući indeks telesne mase i određene komponente upitnika, pokazali su statističku značajnost. **Zaključak.** U ispitivanoj populaciji starijih osoba nije potvrđena povezanost između koncentracije vitamina D i količine visceralnog masnog tkiva. Određeni nutritivni pokazatelji mogu imati značaj u proceni raspodele masnog tkiva.

Cljučne reči: vitamin D; nutritivni status; masno tkivo; intra-abdominalno masno tkivo; sastav tela; starije osobe

IN MEMORIAM IN MEMORIAM



**Prof. dr
SVETLANA S. BUKARICA
(1963–2026)**

Svetlana S. Bukarica rođena je 6. avgusta 1963. godine u Bačkoj Topoli, gde je završila osnovnu školu kao najbolji i odličan đak. Srednju medicinsku školu završila je u Novom Sadu, a 1991. godine diplomirala je na Medicinskom fakultetu, vođena željom da pomaže onima kojima je pomoć najpotrebnija.

Od aprila 1994. godine zaposlila se na Klinici za dečju hirurgiju Instituta za zdravstvenu zaštitu dece i omladine Vojvodine. Tamo je radila predano, savesno i sa neizmernom ljubavlju sve do svog poslednjeg dana, kao vrhunski neonatalni hirurg i dugogodišnji načelnik Odeljenja neonatalne hirurgije.

Bila je i cenjeni vanredni profesor na Medicinskom fakultetu u Novom Sadu, a pet godina je tokom svoje karijere nesebično delila znanje predajući Dečju hirurgiju u Medicinskoj školi u Novom Sadu.

Biti dečji hirurg nije samo posao i profesija. To je sveti poziv koji traži veliko srce, a naša Bukarica je imala upravo takvo srce, dok su joj ruke bile neverovatno blage i nežne. Svakog dana je ulazila u operacionu salu sa jednom jedinom misijom – da spasi ono najvrednije, a to je život deteta. Od onih najmanjih, prevremeno rođenih beba koje su bukvalno nekad manje od dlana, pa sve do adolescenata koji tek ulaze u svet odraslih. Pod svetlima operacione lampe u operacionoj sali, u trenucima kada sekunde odlučuju o životu i smrti, njena ruka je bila savršeno sigurna, a njen um kristalno bistar, kako bi uradila i ono što je izgledalo nemoguće. Bila je poznata, priznata i izuzetno cenjena od svih kolega širom zemlje i regiona. Svi su je gledali sa dubokim strahopoštovanjem. Ne ume i ne usuđuje se svako da bude neonatalni hirurg, niti da se hrabro upusti u lečenje onih najtananih, najosetljivijih pacijenata – novorođenčadi. Ona je to radila sa hirurškom elegancijom i lakoćom koja je odlikovala samo najveće ljude našeg poziva.

Kao šef i koleginica, bila je naš oslonac, naša mirna luka. Kao načelnik Odeljenja neonatalne hirurgije, nosila je ogroman teret odgovornosti, ali nikada

nije dozvolila da se taj pritisak oseti na Odeljenju. Imala je beskrajno poštovanje za ceo tim – od lekara, specijalizanata, pa do medicinskih sestara, tehničara i instrumentarki koje su sa njom delile sate u sali. U najtežim trenucima, tokom dugih, iscrpljujućih i neizvesnih operacija, njen mir i vedar duh donosili su nadu tamo gde je izgledalo da je sve izgubljeno. Zнала je da sasluša svakoga, da razume ljudsku muku i da pomogne bez trunke osude. Nikada joj ništa nije bilo teško, nikada umor i neprospavane noći nisu bili izgovor da se ne uradi apsolutno sve za dobrobit deteta. Od nje smo svakodnevno učili o profesionalizmu, stopostotnoj predanosti pozivu, kolegijalnosti, ali i o čistoj, iskrenoj ljudskosti. Izuzetno je poštovala, cenila i pamtila svoje učitelje, čuvajući tako tradiciju, etiku i čast naše profesije.

Kao prijateljica, Svetlana je bila čist dar, topla, beskrajno odana, diskretna i puna dubokog razumevanja za svaku ljudsku slabost. Imala je tako veseo smeh koji je bio lekovit, smeh koji je u sekundi uspevao da rastera svaku tminu, sumnju i brigu.

Ni jednog jedinog sekunda svog života nije zaboravila odakle je došla, gde je ponikla i gde su njeni koreni. Svi Bačkotopolčani su kod nje imali potpuno poseban tretman, za njih su vrata uvek bila širom otvorena. To se kod Bukarice podrazumevalo bez reči, to je bio njen dug i njena ljubav prema zavičaju.

Ostavila je neizbrisiv, večni trag u Dečjoj bolnici, u našoj medicinskoj nauci, ali pre svega u našim životima i našim srcima. Sva sreća, mnogo je onih koji danas ovim svetom hodaju, trče, raduju se, jer im je ona to svojim znanjem, umećem i junačkim srcem omogućila, pa će njihovi životi biti svedoci njene veličine i njenog postojanja.

Neka joj je večna slava i neizmerno hvala za sve.

Prof. dr Jelena Antić

CIP - Каталогизација у публикацији
Библиотека Матице српске, Нови Сад

61:061(497.113)

MEDICINSKI pregled : časopis Društva lekara Vojvodine Srpskog lekarskog društva = Medical review : journal of the Society of physicians of Vojvodina of the Medical Society of Serbia / glavni i odgovorni urednik Radmila Matijević. – God. 1, br. 1 (1948)- . – Novi Sad : Društvo lekara Vojvodine Srpskog lekarskog društva, 1948- (Novi Sad : Feljton). – 28 cm

Dvomesечно. – Drugo izdanje na drugom nedijumu: Medicinski pregled
(Online) = ISSN 1820-7383

ISSN 0025-8105 = Medicinski pregled

COBISS.SR-ID 3138306

COBISS.SR-ID 331773959

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