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Original scientific paper

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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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ABSTRACT

Liver fibrosis represents an important stage in the progression of chronic liver diseases, and its accurate assessment is essential for prognosis and patient clinical management. Liver biopsy is still considered the gold standard for staging fibrosis, but due to its invasive nature, there is a need for alternative non-invasive and reliable methods. The aim of this study was to evaluate the diagnostic role of the Enhanced Liver Fibrosis (ELF) score in identifying and staging hepatic fibrosis, as well as to analyze its correlation with FibroScan as a reference non-invasive method. The study included 30 patients with chronic liver disease, in whom the ELF score was determined by the measuring the following serological biomarkers: hyaluronic acid, amino-terminal propeptide of type III procollagen (PIIINP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). All patients also underwent a FibroScan examination to assess the severity of hepatic fibrosis. Statistical analysis, were performed using SPSS, version 26.0. The results showed a gradual increase in FibroScan values with increasing ELF score, reflecting a positive relationship between these two methods. A strong and statistically significant correlation was identified at the F3 stage of fibrosis, the early stages the correlation was weaker. No significant differences were found according to age or gender. In conclusion, the ELF score appears to be a valid and reliable tool for the non-invasive assessment of liver fibrosis, particularly in advanced stages, offering the potential to reduce the need for a liver biopsy.

Keywords: ELF score, FibroScan, liver fibrosis, non-invasive liver fibrosis test

INTRODUCTION

Chronic liver diseases represent a major public health problem (Saarinen et al., 2025) and are among the leading causes of death worldwide, with a mortality rate of over one million deaths per year (Higuchi et al., 2022; Sung et al., 2021).

Liver fibrosis is the common final outcome of chronic liver diseases arising from various causes, including chronic viral infection, alcohol consumption, autoimmune disorders, metabolic diseases, hereditary conditions, and fat accumulation and is a dynamic pathological condition characterized by the deposition of collagen fibers due to the activation and transformation of hepatic stellate cells into a fibroblast-like phenotype, along with reduced degradation of the extracellular matrix caused by an imbalance between matrix metalloproteinases and their specific inhibitors (tissue inhibitors of metalloproteinases). This process develops very slowly, and most patients remain asymptomatic. As a result, the condition can easily go unrecognized and untreated for a long time before significant liver damage occurs (Yegin et al., 2019).

Fibrosis detection is essential in the evaluation and treatment of patients with chronic liver lesions. The methods used for examining liver fibrosis are divided into non-invasive and invasive methods (liver biopsy). (Jusufi & Trajkovska, 2024)

Assessment of liver fibrosis is important for evaluating prognosis and determining surveillance strategies for liver cancer. In chronic viral hepatitis, the degree of liver fibrosis is a key parameter for determining antiviral therapy. Currently, liver biopsy is still frequently used as the reference standard for fibrosis assessment; however, it is an invasive procedure associated with patient discomfort and, in rare cases, with serious complications (Friedrich et al., 2010). Liver biopsy offers a direct examination of liver tissue, enabling precise evaluation of steatosis, inflammation, fibrosis, and associated liver damage. This information is essential for patient risk stratification (F0–F1 as low risk and F2–F4 as high risk), for evaluating disease severity, and for developing individualized treatment plans. The METAVIR score is used for staging and monitoring liver fibrosis and inflammation, with the following classification: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa; F3 = numerous septa without cirrhosis; and F4 = cirrhosis (Thallapureddy et al., 2025).

The Enhanced Liver Fibrosis (ELF) test is a non-invasive blood test designed to assess the levels of three key components directly involved in liver matrix metabolism: hyaluronic acid (HA), amino-terminal propeptide of type III procollagen (PIIINP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). Elevated ELF results are associated with biopsy-proven fibrosis and with prognosis for clinically significant outcomes (Day et al., 2019).

The stage of liver fibrosis is widely recognized as an important predictor of clinical outcomes related to liver disease in patients with chronic liver conditions, regardless of etiology. Studies have shown that the ELF score correlates with histological findings in various chronic liver diseases. These findings suggest that ELF can be used as an effective surrogate marker for determining the stage of liver fibrosis (Younossi et al., 2021).

STUDY AIM

The aim of this study is to evaluate the diagnostic role of the ELF score in identifying and staging liver fibrosis by analyzing its biochemical components HA, PIIINP, and TIMP-1, and by comparing the ELF score results with FibroScan findings as a reference non-invasive method for assessing hepatic fibrosis.

MATERIALS AND METHODS

This study was designed to evaluate the diagnostic role of the ELF (Enhanced Liver Fibrosis) score in the identification and staging of liver fibrosis. The study included patients with chronic liver disease of various etiologies who were evaluated at the respective clinical center.

The study was conducted at the University Institute of Clinical Biochemistry-Skopje in collaboration with the University Clinic of Gastroenterohepatology-Skopje. A total of 30 patients were included in the study, of whom 50% were male and 50% were female.The mean age of the patients of both genders was 55.93 ± 14.21 years, with a minimum age of 25 years and a maximum age of 78 years. Of the total number of patients, 63% were aged ≤60 years, while 37% were aged >60 years.

For the measurement of the ELF score, venous blood (serum) was used as the biological material and its determination was performed with the ADVIA Centaur analyzer using the direct chemiluminescent method.

The ELF score test represents a combination of serum biomarkers including HA (hyaluronic acid), PIIINP (amino-terminal propeptide of type III procollagen), and TIMP-1 (tissue inhibitor of matrix metalloproteinases). The analytes are measured automatically and the software calculates and reports a numerical result without units.

All patients underwent liver FibroScan examination, which enabled the determination of the level of hepatic damage and the degree of fibrosis.

Table 1. Diagnostic interpretation of the ELF result according to the stage of hepatic fibrosis

ELF Score		
ELF ≥ 9.00	F2	Significant fibrosis (≥F2) Data indicates that an ELF cutoff of ≥9.00 performs well in NAFLD/NASH populations for the detection of patients with significant fibrosis.
ELF ≥9.80	F3	Advanced fibrosis (≥F3) ≥9.8 is correlated with F3 fibrosis.
ELF ≥11.3	F4	Cirrhosis (F4) 11.3 has high specificity for identifying cirrhosis.

For the processing of the study data, the SPSS software package, version 26.0 for Windows (SPSS, Chicago, IL, USA), was used. For quantitative analysis, measures of central tendency were applied. A two-tailed statistical analysis was performed, and a p-value of < 0.05 was considered statistically significant.

RESULTS

The prospective randomized study was conducted during 2024/2025 at the Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia in collaboration with the University Institute of Clinical Biochemistry and the University Clinic of Gastroenterohepatology at Mother Teresa University Clinical Center-Skopje. For the statistical analysis, measures of central tendency were used, including the mean, median, minimum values, and maximum values, as well as the measures of variability/dispersion, including standard deviation and standard error. A two-tailed analysis was performed to determine statistical significance.

Table 2. Age distribution of patients included in the study (N=30)

N	Mean	Median	SD	Min	Max	Percentiles		
						25th	50th	75th
30	55.93	58.50	14.21	25	78	46.25	58.50	67.75

The age of the patients included in the study ranged from 25 to 78 years. The mean age was 55.9 ± 14.2 years, while the median age was 58.5 years. Percentile values indicate that 25% of the patients were younger than 46.3 years, and 75% were younger than 67.8 years, resulting in an interquartile range (IQR) of 21.5 years. The small difference between the mean and the median suggests a relatively symmetric age distribution, without pronounced extreme values, supporting the use of parametric statistics for describing this variable.

Table 3. Comparison of HA, PIIINP, TIMP-1, and FibroScan by age groups

	≤ 60 (age)					>60 (age)					p value
	N	Min	Max	Mean	SD	N	Min	Max	Mean	SD	
HA	19	10.6	366.47	65.80	80.41	11	34.04	134.13	64.41	34.39	p=0.95
PIIINP	19	4.73	19.18	11.09	4.65	11	5.61	17.57	9.03	3.35	p=0.20
TIMP1	19	155.00	409.00	238.63	75.95	11	155.00	360.00	246.81	59.97	p=0.76
FibroScan	19	7.64	11.83	9.25	1.18	11	8.79	10.80	9.55	0.59	p=0.43

The table presents a comparison of serological biomarkers of liver fibrosis (HA, PIIINP, TIMP-1) and FibroScan values between patients aged ≤60 years and those >60 years, where no statistically significant differences were found between the two groups ($p > 0.05$ for all parameters). The mean HA values were similar in both age groups (65.80 ± 80.41 vs. 64.41 ± 34.39; $p = 0.95$), while PIIINP showed slightly higher values in the ≤60 years group, but without statistical significance (11.09 ± 4.65 vs. 9.03 ± 3.35; $p = 0.20$). No significant differences were observed for TIMP-1 according to age (238.63 ± 75.95 vs. 246.81 ± 59.97; $p = 0.76$), as well as for FibroScan measurements (9.25 ± 1.18 vs. 9.55 ± 0.59; $p = 0.43$). These results suggest that being above or below 60 years of age did not have a significant impact on biomarker levels or the severity of liver fibrosis in this patient group.

Table 4. Distribution of ELF score and FibroScan values according to ELF score categories (<9.0, ≥9.0, ≥9.8, and ≥11.3)

		N	Min	Max	Mean	Median	SD
ELF SCORE	<9.0	10	7.64	8.98	8.32	8.26	0.57
	≥9.0	11	9.01	9.73	9.35	9.30	0.23
	≥9.8	8	9.94	11.01	10.37	10.33	0.37
	≥11.3	1	11.83	11.83	11.83	11.83	0.00
FibroScan	<9.0	10	3.70	31.70	8.82	6.15	8.44
	≥9.0	11	3.80	46.40	12.82	7.80	13.27
	≥9.8	8	4.50	36.50	14.20	8.90	11.60
	≥11.3	1	29.30	29.30	29.30	29.30	0.00

Table 4 presents the distribution of ELF score and FibroScan values according to the defined ELF thresholds (<9.0, ≥9.0, ≥9.8 and ≥11.3). In the ELF <9.0 group (n=10), ELF values were low and homogeneous (mean 8.32 ± 0.57), while FibroScan values in this group showed wide variability (mean 8.82 ± 8.44). In the ELF ≥9.0 category (n=11), there was a gradual increase in ELF score (mean 9.35 ± 0.23), accompanied by an increase in the mean FibroScan values (12.82 ± 13.27). In the ELF ≥9.8 group (n=8), the ELF score was notably higher (mean 10.37 ± 0.37), and FibroScan continued to show a progressive increase in mean values (14.20 ± 11.60). The ELF ≥11.3 category included only one patient, with very high values for both ELF (11.83) and FibroScan (29.30), suggesting advanced fibrosis; however, interpretation of this category is limited due to the very small number of cases. Overall, the data show a trend of increasing FibroScan values with rising ELF score, supporting the correlation between the serological ELF biomarker and the severity of liver fibrosis.

Table 5. Mann–Whitney U test for FibroScan values according to gender

Group	N	Mean Rank
Male	15	16.27
Female	15	14.73
Mann–Whitney U = 101.0; Z = −0.477; p = 0.633		

The Mann–Whitney U test analysis showed no statistically significant difference in FibroScan values between males and females (U = 101.0, Z = −0.477, p = 0.633). The mean rank of FibroScan values was slightly higher in males (Mean Rank = 16.27) compared to females (Mean Rank = 14.73), but this difference did not reach statistical significance. This indicates that the distribution of the fibrosis stages (F0–F4), from minimal fibrosis to advanced fibrosis and cirrhosis, is similar for both genders. This result suggests that the progression and severity of liver fibrosis are not primarily dependent on gender, but are more closely related to pathological changes in liver tissue, such as collagen deposition and structural remodeling.

Table 6. Pearson correlation between ELF score and FibroScan

Variables	Pearson's r	p-value (two-tailed)	N
F1 ELF score –F1 FibroScan	0.402	0.250	10
F2 ELF score –F2 FibroScan	0.132	0.700	11
F3 ELF score –F3 FibroScan	0.866**	0.005	8
F4 ELF score –F4 FibroScan	a	a	1

** Correlation is significant at the 0.01 level (two-tailed)

a Cannot be computed because at least one of the variables is constant

A strong and statistically significant correlation was identified between ELF score and FibroScan in stage F3 (r = 0.866, p = 0.005), reflecting a high agreement between the two methods. In stages F1 and F2, correlations were weak to moderate and did not reach statistical significance, suggesting a more limited discriminative capacity of the ELF score in the early stages of the disease. Correlation analysis for stage F4 was not performed due to the very small number of cases included.

DISCUSSION

FibroTest and ELF can be performed with comparable diagnostic accuracy for non-invasive staging of liver fibrosis. Serum-based tests provide informative results for a larger proportion of patients compared to elastography (Friedrich-Rust et al., 2010). A series of algorithms based on sequential combinations of non-invasive serum markers have demonstrated an accuracy of 93–95% in detecting or excluding liver fibrosis, reducing the need for liver biopsy (Sebastiani & Alberti, 2006).

The usefulness of ELF has been reported in numerous studies, primarily in Western countries, and ELF is recommended as a screening modality for liver fibrosis in Western guidelines. In a study conducted by Tamaki et al. in 2024, they reported a high diagnostic accuracy of ELF across all stages of fibrosis, further reinforcing the value of ELF testing (Tamaki et al., 2024).

Our results showed that being above or below 60 years of age did not affect the levels of serological fibrosis biomarkers (HA, PIIINP, TIMP-1), a finding consistent with the study by Tamaki et al., who reported no age-related influence on ELF values or other non-invasive

markers. They demonstrated that ELF values did not vary according to age in patients with stages F2, F3, and F4 (Tamaki et al., 2024).

Cossiga et al., 2022, in their study, suggested the use of the ELF test as a screening tool in healthcare. If the ELF results are negative, the risk of advanced fibrosis is low. Conversely, if the ELF test indicates the presence of advanced liver fibrosis, the patient should be referred to the hospital for further invasive procedures (Cossiga et al., 2022).

The data from our study shows a positive correlation between ELF score and FibroScan values, where a gradual increase in ELF is associated with increasing severity of liver fibrosis. In patients with ELF <9.0, FibroScan values showed greater variability, while in higher ELF categories, a progressive increase in mean FibroScan values was observed. The patient with ELF ≥11.3 exhibited high values in both methods, suggesting advanced fibrosis, although interpretation is limited due to the small number of cases.

These results support the use of ELF as a reliable indicator of fibrosis stage and the potential for its combination with FibroScan for a more complete non-invasive assessment. Our findings are also consistent with those reported by Gaballah et al. (2015), where ELF test values were higher in advanced fibrosis compared to mild fibrosis, with sensitivity and specificity of 86% and 92.9%, respectively. This study emphasizes that the implementation of the ELF test could potentially replace liver biopsy and be used to monitor treatment efficacy.

CONCLUSION

The results of this study indicate that the ELF score represents a reliable non-invasive method for the assessment and staging of liver fibrosis. A strong and statistically significant correlation was observed between ELF score and FibroScan in advanced fibrosis (F3), confirming the compatibility of these two methods. In the early stages of fibrosis, the discriminative capacity of the ELF score was more limited, suggesting the need for its combination with other diagnostic methods. Overall, the ELF score can be used as a valuable tool in clinical practice for non-invasive screening and monitoring of liver fibrosis, reducing the need for liver biopsy.

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Original scientific paper

ASSOCIATION OF SERUM 25-HYDROXYVITAMIN D WITH C-REACTIVE PROTEIN ACROSS BODY MASS INDEX CATEGORIES IN ADULTS

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ABSTRACT

Background: Vitamin D insufficiency and systemic inflammation frequently coexist with excess adiposity, but their relationship across the full body mass index (BMI) spectrum remains incompletely characterized.

Aim: To evaluate serum 25-hydroxyvitamin D [25(OH)D] and C-reactive protein (CRP) across BMI categories and determine whether CRP is independently associated with 25(OH)D.

Methods: This cross-sectional analysis included 200 adults allocated to five BMI groups (normal weight, overweight, obesity class I, obesity class II, and obesity class III; n = 40 per group). Group differences were tested with Kruskal–Wallis analysis and post hoc multiple comparisons. Associations between CRP and 25(OH)D were assessed using Spearman correlation in the total sample and BMI strata. A multivariable linear regression model adjusted for age, sex, smoking, BMI, triglycerides, high- and low-density lipoprotein cholesterol, glycated hemoglobin, and insulin resistance.

Results: Serum 25(OH)D decreased markedly across BMI categories ($H = 139.74$, $p < 0.001$), whereas CRP increased ($H = 122.68$, $p < 0.001$). The pooled association between CRP and 25(OH)D was strong and inverse ($\rho = -0.68$, $p < 0.001$). The association remained significant in normal-weight participants ($\rho = -0.78$, $p < 0.001$), participants with overweight ($\rho = -0.50$, $p < 0.001$), and the combined obesity group ($\rho = -0.24$, $p = 0.008$). The multivariable model was significant ($R^2 = 0.528$; adjusted $R^2 = 0.502$; $p < 0.001$), and CRP remained independently associated with lower 25(OH)D ($B = -0.483$, standardized $\rho = -0.211$, $p < 0.001$).

Conclusions: Higher BMI was accompanied by lower 25(OH)D and higher CRP. The inverse CRP–25(OH)D relationship persisted after adjustment for demographic and metabolic covariates, although the cross-sectional design does not establish causality.

Keywords: obesity; inflammation; adiposity; cardiometabolic risk; hypovitaminosis D

INTRODUCTION

Obesity is a major public-health challenge and is closely associated with metabolic dysfunction, insulin resistance, dyslipidemia, type 2 diabetes, and cardiovascular disease. A central biological feature of excess adiposity is systemic inflammation driven by adipocyte dysfunction, immune-cell infiltration, and altered cytokine signaling (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; World Health Organization, 2000). C-reactive protein (CRP), an acute-phase protein produced predominantly by the liver, is widely used as an accessible marker of inflammatory activity (Pepys & Hirschfield, 2003).

Vitamin D is classically involved in calcium and bone homeostasis but also participates in immune and

metabolic regulation. Serum 25-hydroxyvitamin D [25(OH)D] is the accepted indicator of vitamin D status because it reflects endogenous synthesis and dietary exposure (Holick, 2007). Low 25(OH)D concentrations are common in people with overweight and obesity. Proposed explanations include volumetric dilution, sequestration within adipose tissue, lower sun exposure, reduced physical activity, and obesity-related metabolic changes (Vanlint, 2013; Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). Meta-analytic and genetic evidence supports a directional effect of greater adiposity on lower circulating 25(OH)D (Pereira-Santos, Costa, Assis, Santos, & Santos, 2015; Vimaleswaran et al., 2013).

Observational studies have also reported inverse associations between 25(OH)D and CRP (Amer & Qayyum, 2012; Yang et al., 2020). Nevertheless, this relationship is complex. Adiposity may confound or mediate part of the association, and randomized trials have not consistently shown that vitamin D supplementation reduces inflammatory biomarkers in adults with overweight or obesity (Gouveia et al., 2024; Rafiq et al., 2020). Evaluation across clearly defined BMI categories, together with multivariable adjustment, may help distinguish the contribution of inflammatory activity from the broader metabolic phenotype.

The aim of this study was to compare serum 25(OH)D and CRP concentrations across five BMI categories and to assess the overall, stratum-specific, and independently adjusted association between CRP and 25(OH)D in adults. We hypothesized that increasing BMI would be accompanied by lower 25(OH)D and higher CRP and that CRP would remain inversely associated with 25(OH)D after adjustment for relevant demographic and metabolic variables.

METHODS

Study design and participants

A cross-sectional observational analysis was performed using the doctoral research database. The dataset contained 200 adults aged 23–65 years, with 40 participants in each of five BMI categories: normal weight (Group 1), overweight (Group 2), obesity class I (Group 3), obesity class II (Group 4), and obesity class III (Group 5). Each group included 20 women and 20 men. The equal group sizes reflect the study design and should not be interpreted as population prevalence estimates.

Body weight and height were recorded using standardized anthropometric procedures, and BMI was calculated as weight in kilograms divided by height in metres squared. The categories followed conventional World Health Organization thresholds: normal weight, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obesity class I, 30.0–34.9 kg/m^2; obesity class II, 35.0–39.9 kg/m^2; and obesity class III, ≥40.0 kg/m^2.

Laboratory variables

Fasting venous blood samples were collected after a 12-hour overnight fast and analyzed at the Private Health Institution Diagnostic Biochemical Laboratory, Molecular Diagnostics Laboratory and Diagnostic Microbiological Laboratory RAMUS, Skopje, Republic of North Macedonia, using validated laboratory procedures. Serum 25(OH)D was measured by chemiluminescent immunoassay (CLIA) as the principal indicator of vitamin D status, and CRP was analyzed as the marker of systemic inflammatory activity. Triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), and the homeostatic model assessment of insulin resistance (HOMA-IR) were included as covariates in the multivariable analysis.

All clinical and laboratory information was analyzed in anonymized form. The study procedures were reported as compliant with the Declaration of Helsinki, and participants provided informed consent in the original doctoral protocol.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (range), depending on distribution, and categorical variables as number and percentage. Between-group differences were assessed with Kruskal–Wallis analysis of variance by ranks; significant omnibus tests were followed by post hoc multiple comparisons. Smoking status was compared using the Pearson chi-square test.

Spearman rank correlation coefficients (ρ) were calculated for the association between CRP and 25(OH)D in the total sample, the normal-weight group, the overweight group, and the combined obesity classes I–III. A multivariable linear regression model was constructed with 25(OH)D as the dependent variable and age, sex, smoking status, BMI, triglycerides, HDL-C, LDL-C, CRP, HbA1c, and HOMA-IR as predictors. Results are reported as unstandardized coefficients (B), standard errors, standardized coefficients (β), 95% confidence intervals (CI), and p-values. All tests were two-sided, and $p < 0.05$ was considered statistically

significant. Values reported by the software as p = 0.000 are presented as p < 0.001.

RESULTS

Participant characteristics and between-group differences

The five groups differed significantly in age, smoking status, BMI, serum 25(OH)D, and CRP (Table 1). The normal-weight group was younger and contained fewer current smokers than several higher-BMI groups. Median 25(OH)D declined from 62.25 ng/mL in the normal-weight group to 8.35 ng/mL in obesity class III, whereas median CRP increased from 0.95 to 10.15 mg/L.

Table 1. Participant characteristics across BMI categories

Characteristic	Normal weight (n=40)	Overweight (n=40)	Obesity I (n=40)	Obesity II (n=40)	Obesity III (n=40)	Overall p
Women, n (%)	20 (50.0)	20 (50.0)	20 (50.0)	20 (50.0)	20 (50.0)	1.000
Age, years	38.63 ± 12.07	45.15 ± 12.06	51.98 ± 11.55	49.05 ± 11.01	46.13 ± 10.44	<0.001
Current smokers, n (%)	16 (40.0)	24 (60.0)	30 (75.0)	20 (50.0)	25 (62.5)	0.022
BMI, kg/m²	23.04 ± 1.51	27.55 ± 1.26	32.68 ± 1.37	37.49 ± 1.38	46.99 ± 7.61	<0.001
25(OH)D, ng/mL	62.25 (35.60–72.40)	27.65 (7.22–37.60)	12.40 (7.14–18.30)	10.65 (3.40–17.60)	8.35 (3.40–11.50)	<0.001
CRP, mg/L	0.95 (0.50–1.80)	2.10 (1.00–81.00)	4.25 (1.00–32.20)	8.30 (1.00–27.90)	10.15 (1.00–70.40)	<0.001

Values are mean ± SD, median (range), or n (%).

Serum 25(OH)D across BMI categories

The overall difference in serum 25(OH)D was significant (Kruskal–Wallis H[4, N = 200] = 139.74, p < 0.001). Mean ranks decreased stepwise from 180.44 in normal weight to 38.98 in obesity class III. Normal-weight participants had higher 25(OH)D than every other group (all p < 0.001). Participants with overweight had higher concentrations than those with obesity class I (p = 0.040), class II (p < 0.001), and class III (p < 0.001). Obesity class I also had higher concentrations than class III (p = 0.002); the remaining pairwise contrasts were not significant. Figure 1 shows the progressive decline in median values.

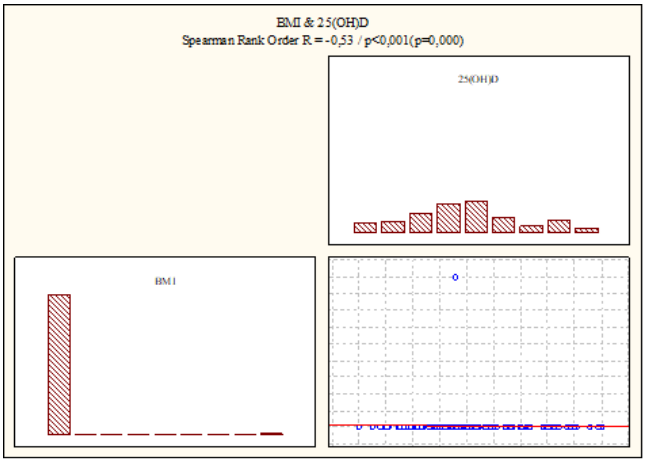


Figure 1. Median serum 25(OH)D concentrations across BMI categories. Ranges are reported in Table 1.

C-reactive protein across BMI categories

CRP differed significantly across groups (Kruskal–Wallis H[4, N = 200] = 122.68, p < 0.001), with mean ranks increasing from 26.35 in normal weight to 154.26 in obesity class III. CRP was lower in normal weight than in all higher-BMI groups (all p < 0.001). The overweight group had lower CRP than obesity class II and III (both p < 0.001), and obesity class I had lower CRP than obesity class III (p = 0.004). Other pairwise contrasts were not statistically significant. Median values are shown in Figure 2.

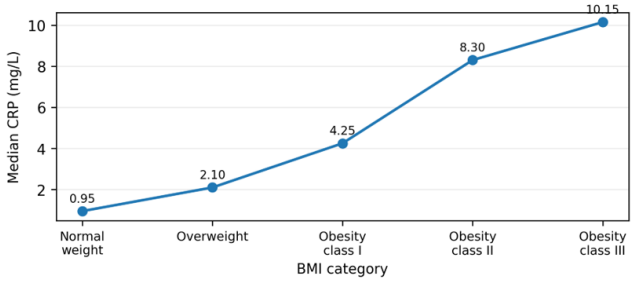


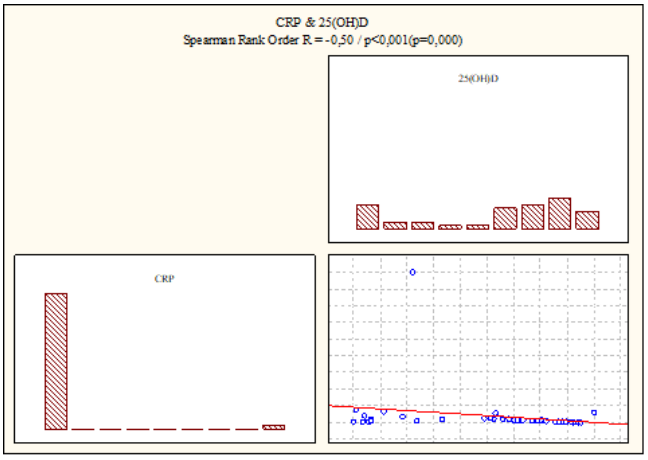
Figure 2. Median serum CRP concentrations across BMI categories. Ranges are reported in Table 1.

Association between CRP and 25(OH)D

In the total sample, CRP and 25(OH)D were strongly and inversely correlated ($\rho = -0.68$, p < 0.001). The association remained significant within the prespecified BMI strata, although its magnitude decreased with greater adiposity: strong in normal weight, moderate in overweight, and weak in the combined obesity group (Table 2).

Table 2. Spearman correlations between CRP and 25(OH)

Population	n	Spearman ρ	p
Total sample	200	−0.68	<0.001
Normal weight	40	−0.78	<0.001
Overweight	40	−0.50	<0.001
Obesity classes I–III combined	120	−0.24	0.008



Multivariable linear regression

The multivariable model was statistically significant ($R = 0.726$, $R^2 = 0.528$, adjusted $R^2 = 0.502$; $F = 20.654$, $p < 0.001$). After adjustment, higher CRP remained independently associated with lower 25(OH)D ($B = −0.483$, standardized $\beta = −0.211$, $p < 0.001$). Age, triglycerides, HDL-C, LDL-C, and HbA1c were also significant independent predictors, whereas sex, smoking status, BMI, and HOMA-IR were not significant in this model (Table 3).

Table 3. Multivariable linear regression with serum 25(OH)D as the dependent variable (N = 200)

Predictor	B	SE	ρ	95% CI for B	p
Sex (1)	1.472	2.205	0.036	−2.878 to 5.821	0.505
Age	−0.334	0.091	−0.198	−0.514 to −0.154	<0.001
Smoking (1)	−2.333	2.231	−0.056	−6.734 to 2.068	0.297
BMI	−0.00004	0.000	−0.005	−0.001 to 0.001	0.918
Triglycerides	−7.226	1.314	−0.366	−9.819 to −4.633	<0.001
HDL-C	−5.744	2.719	−0.139	−11.108 to −0.380	0.036
LDL-C	−5.803	1.397	−0.266	−8.559 to −3.046	<0.001
CRP	−0.483	0.124	−0.211	−0.729 to −0.238	<0.001
HbA1c	−2.443	1.145	−0.144	−4.703 to −0.183	0.034
HOMA-IR	−0.046	0.058	−0.043	−0.160 to 0.067	0.424

B, unstandardized coefficient; β, standardized coefficient; CI, confidence interval. Binary-variable coding follows the original study database.

DISCUSSION

This study demonstrated a clear gradient across BMI categories: serum 25(OH)D declined as adiposity increased, whereas CRP increased. The central finding was a strong inverse association between CRP and 25(OH)D in the total sample. Importantly, the relationship was not limited to the pooled data; it remained significant in normal-weight, overweight, and obese participants, although the correlation weakened across the higher-BMI strata. CRP also remained an independent negative predictor of 25(OH)D after adjustment for demographic, lipid, glycemic, and insulin-resistance variables.

The progressive reduction in 25(OH)D is consistent with the established association between adiposity and lower vitamin D status. Reduced bioavailability due to distribution into a larger body compartment and retention in adipose tissue are plausible mechanisms (Vanlint, 2013; Wortsman et al., 2000). The systematic review by Pereira-Santos et al. (2015) showed a higher frequency of vitamin D deficiency in obesity, while Mendelian-randomization evidence suggested that higher BMI contributes causally to lower 25(OH)D (Vimaleswaran et al., 2013). The present stepwise pattern across five BMI categories supports a dose-related association, but the cross-sectional design cannot determine temporal direction.

The rise in CRP with BMI is biologically plausible because adipose-tissue expansion promotes macrophage recruitment and pro-inflammatory cytokine signaling (Ellulu et al., 2017). The inverse CRP–25(OH)D association agrees with population-based findings from Amer and Qayyum (2012) and Yang et al. (2020). The persistence of the association after adjustment suggests that CRP captures information not fully represented by BMI alone. Nevertheless, Rafiq et al. (2020) reported that adiposity explained a substantial part of the vitamin D–inflammation relationship, emphasizing that residual confounding and pathway overlap remain possible.

The lower stratum-specific correlation in obesity may reflect restricted ranges of 25(OH)D among participants with obesity, biological heterogeneity, or floor effects at very low concentrations. It may also indicate that additional determinants—such as season, sunlight exposure, dietary intake, supplement use, comorbidities, and medication—become increasingly important once severe adiposity is established. Therefore, the pooled coefficient should not be interpreted as uniform across all BMI levels.

The findings support clinical awareness that low 25(OH)D and elevated CRP can coexist in adults with excess adiposity, but they do not establish that vitamin D supplementation will reduce inflammation. A recent meta-

analysis of randomized trials in adults with overweight or obesity found no significant effect of isolated vitamin D supplementation on CRP, interleukin-6, or tumor necrosis factor concentrations (Gouveia et al., 2024). Accordingly, vitamin D and CRP should be interpreted within the broader clinical and metabolic context rather than used as evidence of a direct therapeutic pathway.

Strengths of the study include the balanced number of participants across five BMI categories, equal sex distribution within groups, analysis across a wide BMI range, stratum-specific correlations, and multivariable adjustment. Several limitations require consideration. The cross-sectional design precludes causal inference, and the stratified equal-size sampling prevents estimation of population prevalence. Age and smoking differed across groups, although both were included in the regression model. Seasonal exposure, diet, supplements, physical activity, and detailed comorbidity information were not available for the present analysis. CRP values reached 81.0 mg/L in the overweight group and 70.4 mg/L in obesity class III; without repeat measurements or clinical adjudication, acute inflammatory contributors cannot be excluded in all participants. Finally, the pooled correlation may partly reflect separation among the prespecified BMI groups.

CONCLUSIONS

Increasing BMI was associated with progressively lower serum 25(OH)D and higher CRP. CRP showed a significant inverse association with 25(OH)D in the total sample and within BMI strata and remained independently associated after multivariable adjustment. These findings identify a close observational relationship between vitamin D status, adiposity, and inflammatory activity, but prospective studies with repeated CRP measurements and detailed assessment of seasonal, lifestyle, and treatment factors are required to clarify causality and clinical implications.

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Profesional paper

PARAMETRAT KLINIKË DHE LIDHJA E TYRE ME STILIN E JETESËS TE PACIENTËT ME ARTRIT REUMATOID NË TRAJTIM ME ETANERCEPT

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ABSTRAKTI

Hyrja: Artriti reumatoid është sëmundje kronike sistemike, e cila manifestohet me dhimbje dhe rënie të funksionalitetit tek këta pacientë. Faktorët e stilit të jetës mund të luajnë një rol në menaxhimin e sëmundjes. Qëllimi: Ky punim ka për qëllim të pasqyrojë parametrat klinikë (dhimbja, funksionaliteti dhe aktiviteti i sëmundjes) dhe lidhjen ndërmjet tyre dhe faktorëve të stilit të jetesës. Metodologjia: Në hulumtim janë përfshirë 50 pacientë me artrit reumatoid, që ishin duke u trajtuar me etanercept gjatë periudhës shtator 2023 - shkurt 2024 në Qendrën Klinike Universitare të Kosovës. U grumbulluan të dhëna sociodemografike, të dhëna për stilin e jetesës, dhimbjen, funksionalitetin dhe aktivitetin e sëmundjes. Të dhënat u analizuan me programin SPSS.

Rezultatet: Pjesa më e madhe e pacientëve ishin të gjinisë femrore, me moshë mesatare 41.8 vjeç. 40% e tyre kishin indeks të masës trupore mbi nivelin normal derisa koha mesatare e realizimit të aktivitetit fizik në javë ishte 28.9 minuta. Analiza e korrelacionit tregoi lidhje statistikisht të rëndësishm në mes të aktivitetit fizik dhe BMI-së, dhimbjes, aktivitetit të sëmundjes dhe funksionalitetin ($p<0.05$). Përfundimi: Hulumtimi ynë konfirmon se faktorët e stilit të jetës tek pacientët me artrit reumatoid luajnë një rol të rëndësishëm në mirëqenien e tyre. Aktiviteti fizik dhe indeksi i masës trupore kanë lidhje të besueshme me dhimbjen, funksionalitetin dhe aktivitetin e sëmundjes.
Fjalët kyçe: artriti reumatoid, stili i jetës, parametrat klinikë

HYRJE

Artriti reumatoid (AR) është një nga sëmundjet më të zakonshme autoimune kronike inflamatore e cila karakterizohet nga dhimbja dhe ënjtja simetrike, poliartikulare, që zakonisht përfshijnë nyjet e vogla të duarve dhe këmbëve. (1) Në Evropë dhe Amerikën e Veriut, prevalenca e AR është 0,5-1,0%. Prek të paktën dy herë më shumë gjinin femrore dhe mund të shfaqet në çdo moshë. (1,2) Shkaqet e AR janë ende të paqarta, edhe pse vitet e fundit është bërë përparim i rëndësishëm. Tanimë është bërë evidente se AR zhvillohet në bazë të komponentëve gjenetikë, por edhe faktorët e jashtëm luajnë një rol të rëndësishëm. (3) AR është një sëmundje simetrike poliartikulare që përfshin nyje të shumta dhe të dyanshme. Në një pacient me AR zakonisht paraqiten dhimbja dhe edema në nyjet e duarve dhe këmbëve. Ënjtja është kryesisht në kyçet e duarve dhe nyjet metakarpofalangeale, interfalangeale proksimale dhe metatarsofalangeale. Kjo mund të shoqërohet me ngurtësim të nyjeve në mëngjes që zgjat më shumë se 30 minuta dhe zakonisht deri në disa orë. Ënjtja zakonisht është "e butë" për shkak të sinovitit dhe efuzionit, në kontrast me ënjtjet "e forta" (kockore) të osteoartritit. Mund të përfshihen pjesa e kyçit të dorës dhe po ashtu edhe nyjet më të mëdha si të kërdhokullave, gjurit, bërrylit dhe shpatullave. Ky inflamacion shkakton ndryshime edhe në hapësirën intra-artikulare duke shkaktuar ngushtim e deri në ankillozë të nyjës së atakuar. (4-7) Në figurën 1, janë paraqitur stadet e zhvillimit të AR e manifestuar me ndryshimet radiologjike të tij në nyjet e shuplakës së dorës, nga faza e hershme e deri në fazën e fundit ku zhvillohen deformime dhe ankilloza nyjore. (7)

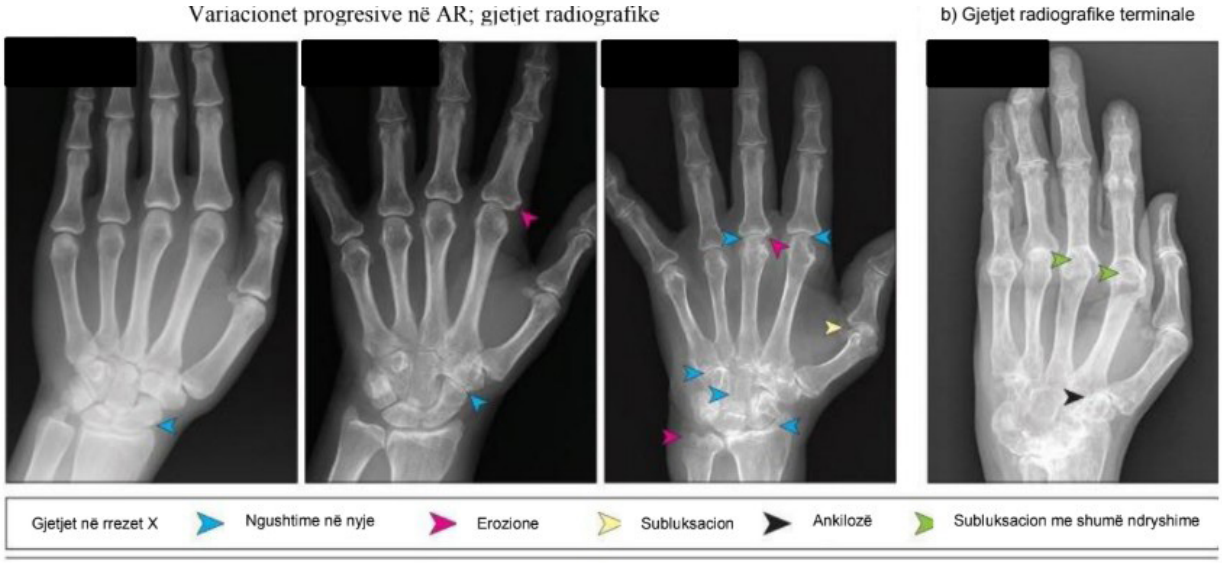

Figura 1. Stadet e zhvillimit të artritit reumatoid

Medikamentet antireumatike modifikuese të sëmundjes (DMARDs), duke përfshirë ato biologjike (bDMARDs), si etancerepcti janë një opsion i pranueshëm për trajtimin e AR dhe ofrojnë një terapi të synuar në strukturat e sistemit imunitar. (8) Aleanca Evropiane e Shoqatave të Reumatologjisë (EULAR) ka rekomanduar se përveç trajtimit medikamentoz, menaxhimi i artritit inflamator duhet të fokusohet edhe në faktorët e stilit të jetës si aktiviteti fizik dhe ushtrimet, kontrolli i peshës trupore, ushqyerja e shëndetshme, ndërprerja e duhanpirjes dhe një mënyrë aktive e jetesës Këta parametra mund të kenë rol në menaxhimin e dhimbjes, aktivitetit të sëmundjes, funksionalitetit dhe kualitetit të jetës. (9,10)

QËLLIMI

Ky punim ka për qëllim të vlerësojë parametrat klinikë, si dhimbjen, funksionalitetin dhe aktivitetin e sëmundjes, si dhe të analizojë lidhjen e këtyre parametrave me faktorët e stilit të jetesës.

METODOLOGJIA

Gjithsej 50 pacientë të njëpasnjëshëm me artrit reumatoid nga Klinika e Reumatologjisë në Qendrën Klinike Universitare të Kosovës (QKUK) u përfshinë në hulumtim në periudhën shtator 2023 - shkurt 2024. Në studim janë përfshirë pacientët që ishin të diagnostikuar të paktën tre muaj më parë nga reumatologu me AR sipas kritereve të Kolegjit Amerikan të Reumatologjisë/EULAR (11) dhe që ishin nën trajtim me etanercept. Kriteret përjashtuese të studimit ishin: AR juvenil, pacientët më të rinj se 16 vjeç, pacientët me fraktura ose lëndime traumatike dhe gratë shtatzëna. Janë grumbulluar të dhënat sociodemografike si gjinia, mosha, dhe kohëzgjatja e sëmundshmërisë. Statusi funksional te pacientët me AR është matur përmes Indeksit të Paaftësisë të Pyetësorit të Vlerësimit Shëndetësor (HAQ-DI) (12), raportimi i nivelit të dhimbjes është bërë përmes Visual Analogue Scale (VAS) (13), derisa aktiviteti i sëmundjes tek pacientet me AR është matur me Disease Activity Score 28 (DAS28). (14) Analiza statistikore është realizuar përmes programit SPSS. Çdo pjesëmarrës në hulumtim ka plotësuar formularin e pëlqimit për pjesëmarrje në hulumtim. Të dhënat janë trajtuar në mënyrë anonime dhe konfidenciale. Është marrë leja për hulumtim nga Komisioni Etik i Fakulteti të Mjekësisë të Universitetit të Prishtinës (Ref.nr 4542), dhe leje nga Zyra për Mbrojtjen e të dhënave personale nga Qendrës Klinike Universitare të Kosovës - Shërbimi Spitalor dhe Klinik Universitar i Kosovës (Nr.Protokolli 3425).

REZULTATET

Në hulumtimin tonë janë përfshirë 50 pacientë me artrit reumatoid. Pjesa më e madhe e pacientëve ishin të gjinisë femrore (64%), derisa mosha mesatare e tyre ishte 41.8 vjeç, me devijim standard 7.8. Kohëzgjatja mesatare e sëmundjes ishte 7.5 vjeç. Gjithashtu, 70% e pacientëve kishin përfunduar shkollën e mesme, dhe shumica e tyre (64%) ishin të punësuar, tabela 1.

Tabela 1. Karakteristikat sociodemografike të pacientëve me artrit reumatoid

Karakteristikat	N	%
Gjinia		
Femër	32	64.0
Mashkull	18	36.0
Mosha		
Min-max, Mean (SD)		
	22-66	41.8 (7.8)
Kohëzgjatja e sëmundjes	1-12	7.5 (4.3)
Edukimi		
I mesëm	35	70.0
Universitar	15	30.0
Vendbanimi		
Rural	37	74.0
Urban	13	26.0
Punësimi		
I/e punësuar	32	64.0
I/e papunësuar	16	32.0
Pensionuar	2	4.0

Të dhënat në lidhje me faktorët e stilit të jetës janë paraqitur në tabelën 2. Sipas rezultateve tona, koha mesatare e realizimit të aktivitetit fizik në javë te pacientë me artrit reumatoid ishte 28.9 minuta me devijim standard 11.2 minuta. Niveli minimal dhe maksimal i realizimit të aktivitetit fizik ishte 15-90 minuta. Sa i përket duhanpirjes, 44% e pacientëve deklaruan se janë duhanpirës, ndërsa sa i përket indeksit të masës trupore, 44% e pacientëve kishin BMI normale, 38% ishin mbipeshë dhe 14% obezë, tabela 2.

Tabela 2. Faktorët e stilit të jetës të pacientëve me artrit reumatoid

Karakteristikat	N	%
Aktiviteti fizik (minuta për javë)		
Min-max, Mean (SD)	15-90	28.9 (11.2)
Duhanpirja		
Po	22	44.0
Jo	28	56.0
BMI		
Nënpeshë	2	4.0
Normale	22	44.0
Mbipeshë	19	38.0
Obezë	7	14.0

Niveli mesatar i dhimbjes tek pacientët me artrit reumatoid ishte 4.1 me devijim standard 2.6 dhe me vlera minimale dhe maksimale prej 3 dhe 8 pikësh nga 10. Për më shumë, 32% e pacientëve kishin remision të sëmundjes, 28% aktivitet të ulët të sëmundjes, 22% kishin aktivitet të moderuar të sëmundjes dhe 18% aktivitet të lartë të sëmundjes. Gjithashtu, 36% e pacientëve deklaruan se kanë aftësi të lehta dhe vështirësi mesatare të funksionalitetit, derisa 38% e tyre deklaruan se kanë paaftësi mesatare deri të rëndë të funksionalitetit, tabela 3.

Tabela 3. Parametrat klinik tek pacientët me artrit reumatoid

Karakteristikat	N	%
Dhimbja		
Min-max, Mean (SD)	3-8	4.1 (2.6)
Aktiviteti i sëmundjes (DAS28)		
Remision	16	32.0
Aktiviteti i ulët i sëmundjes	14	28.0
Aktiviteti i moderuar i sëmundjes	11	22.0
Aktiviteti i lartë i sëmundjes	9	18.0
Funksionaliteti (HAQ-DI)		
Aftësi të lehta ose me vështirësi mesatare	18	36.0
Paaftësi mesatare deri në të rëndë	19	38.0
Paaftësi të rëndë deri shumë të rëndë	13	26.0

Në rezultatet e hulumtimit tonë, dhimbja kishte korelacion pozitiv me aktivitetin e sëmundjes (r = 0.512, p = 0.0025), funksionalitetin (r = 0.326, p = 0.038) dhe BMI-në (r = 0.463, p = 0.0048), ndërsa me aktivitetin fizik u gjet korelacion negativ (r = -0.298, p = 0.046). Aktiviteti i sëmundjes kishte korelacion pozitiv me funksionalitetin (r = 0.356, p = 0.012) dhe BMI-në (r = 0.502, p = 0.031), ndërsa korelacion negativ me aktivitetin fizik (r = -0.312, p = 0.031). Për më shumë, funksionaliteti rezultoi me korelacion pozitiv me BMI-në (r = 0.410, p = 0.039) dhe korelacion negativ me aktivitetin fizik (r = -0.301, p = 0.032). Një korelacion negativ u evidentua edhe ndërmjet BMI-së dhe aktivitetit fizik (r = -0.426, p = 0.027). Kjo nënkupton se, me rritjen e BMI-së, përkeqësohen parametrat klinikë, përkatësisht rritet niveli i dhimbjes, ulet funksionaliteti dhe rritet aktiviteti i sëmundjes. Në të kundërt, rritja e aktivitetit fizik lidhet me përmirësimin e këtyre parametrave klinikë te pacientët me artrit reumatoid, tabela 4.

Tabela 4. Analiza e korelacionit në mes të parametrave klinik dhe stilit të jetës tek pacientët me artrit reumatoid

Correlations							
			Dhimbja	Aktiviteti i sëmundjes	Funksionaliteti	BMI	Aktiviteti fizik
Spearman's rho	Dhimbja	Correlation Coefficient	1	.512	.326	.463	-.298
		Sig. (2-tailed)	.	0.0025	0.038	0.0048	0.046
		N	50	50	50	50	50
	Aktiviteti i sëmundjes	Correlation Coefficient	.512	1	.356	.502	-312
		Sig. (2-tailed)	0.0025	.	0.012	0.031	0.031
		N	50	50	50	50	50
	Funksionaliteti	Correlation Coefficient	0.326	.356	1	.410	-.301
		Sig. (2-tailed)	0.038	0.012	.	0.039	0.032
		N	50	50	50	50	50
	BMI	Correlation Coefficient	0.463	.502	.410	1	-426
		Sig. (2-tailed)	0.0048	0.031	0.039	.	0.027
		N	50	50	50	50	50
	Aktiviteti fizik	Correlation Coefficient	-.298	-312	-.301	-426	1
		Sig. (2-tailed)	0.046	0.031	0.032	0.027	.
		N	50	50	50	50	50
p<0.05							

DISKUTIMI

Hulumtimi ynë kishte për qëllim të vlerësonte parametrat klinikë dhe lidhjen e tyre me stilin e jetesës te pacientët me artrit reumatoid. Studimi ynë konfirmon se ekziston një lidhje statistikisht e rëndësishme ndërmjet parametrave klinikë dhe faktorëve të stilit të jetës te pacientët me AR. Sa më i lartë të jetë BMI-ja, aq më të larta priren të jenë nivelet e dhimbjes, paaftësisë dhe aktivitetit të sëmundjes, dhe sa më i lartë niveli i aktivitetit fizik aq më e vogël do të jetë dhimbja, paaftësia dhe aktiviteti i sëmundjes. Një studim i realizuar në Holandë nga Molenar et al., ka përfshirë 186 pacientë me artrit reumatoid. Ky studim konfirmoi se dhimbja tek pacientët me AR kishte lidhshmëri me statusin funksional apo paaftësinë. (15) Gjithashtu, edhe autori Sokka et al., në një hulumtim të realizuar në Finlandë me 141 pacientë me AR e konfirmoi rolin e dhimbjes në funksionalitet tek këta pacientë. (16) Gjetjet e këtyre studimeve përputhen me rezultatet tona se dhimbja dhe funksionaliteti janë të ndërlidhura tek pacientët me AR.

Studimi nga autorja Nikiphorou et al., në Mbretërinë e

Bashkuar, konfirmon lidhshmërinë në mes të obezitetit dhe dhimbjes, funksionalitetit dhe kualitetit të jetës tek pacientët me artrit reumatoid. (17) Një rishikim sistematik me meta-analizë ka konkluduar se obeziteti mund të ketë rol në remisionin e sëmundjes dhe ka rekomanduar që BMI-ja të vlerësohet gjatë menaxhimit të sëmundjes nga profesionistët shëndetësorë. (18) Gjithashtu, edhe studimet e tjera e konfirmojnë se aktiviteti fizik ka lidhshmëri me dhimbjen, paaftësinë, aktivitetin e sëmundjes dhe kualitetin e jetës tek pacientët me AR. (19, 20)

PËRFUNDIMI DHE REKOMANDIMET

Hulumtimi ynë tregon se faktorët e stilit të jetës te pacientët me artrit reumatoid luajnë një rol të rëndësishëm në mirëqenien e tyre. Aktiviteti fizik dhe indeksi i masës trupore kanë lidhje statistikisht të rëndësishme me dhimbjen, funksionalitetin dhe aktivitetin e sëmundjes. Aktiviteti fizik dhe indeksi i masës trupore duhet të monitorohen gjatë trajtimit të pacientëve me artrit reumatoid.

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Profesional paper

КОНГЕНИТАЛНИ НАРУШУВАЊА НА ЗГЛОБОТ НА КОЛКОТ MORBUS LEGG-CALVE-PERTHES (LCPB)

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АПСТРАКТ

ВОВЕД: Јувенилните остеохондрози претставуваат идиопатски, развојни пореметувања настанати како резултат на присутните циркулаторни нарушувања и последична појава на аваскуларна (асептична) некроза и пореметување на енхондралната осификација (хондогенеза и остеогенеза)во предел на примарните и секундарните јадра на осификацијата на зглобот. Legg-Calve-Perthes (LCPB) претставува примарен остеохондритис на колкот, болест со се уште непозната етиологија.

ЦЕЛ: Целта на студијата е да се проценат клиничките и радиографските резултати, ефикасноста, безбедноста и долгорочните резултати во лекувањето и третманот при просечно 5 годишно следење.

МЕТОДОЛОГИЈА НА ИСТРАЖУВАЊЕТО: Студијата претставува ретроспективна студија, за чие реалиизрање се користени податоци од пациенти со дијагностициран јувенилен остеохондрит, третирани во "Св. Еразмо"– специјална болница за ортопедија и трауматологија во Охрид во периодот од 2000 до 2010 година. Истражувачката популација е дефинирана како деца на возраст од 2 до 14 години, со работна дијагноза primaren osteohondritis na kolkot, односно болеста на Legg-Calve-Perthes (LCPB). Големината на примерокот, односно контингентот на испитаници ќе го сочинуваат 56 пациенти со примарен остеохондритис на колкот.

РЕЗУЛТАТИ: Резултатите на оваа студија во лекувањето на дел од пациентите заболени од примарен остеохондритис на колкот, односно болеста на Legg-Calve-Perthes (LCPB) во Р. Македонија во периодот од 2000 до 2010 година, укажуваат на нејзината застапеност во однос на одредените класификациони групи, демографските и биомедицинските карактеристики, хередитетот и нејзината прогресија. Во истражувањето беа вклучени и анализирани 56 испитаници, пациенти на возраст од 2 до 14 години, со дијагностициран јувенилен остеохондрит на главата на бутната коска (болест на Legg-Calve-Perthes). Половата структура на испитаниците ја сочинуваа 37 (66.07%) машки пациенти и 18 (32.14%) женски пациенти.

ЗАКЛУЧОК: Болеста на Legg-Calve-Pertes (LCP) е актуелна тема во областа на детската ортопедија пред се поради високиот морбидитет и не ретко нејасната прогноза на болеста. Годишно 1 од 10 000 деца развиваат аваскуларна некроза на ниво на епифизата на главата на бутната коска (41). Лекувањето на пациентите со болеста на Legg-Calve-Pertes (LCP) е долготрајно, а успехот од лекувањето и третманот е директно поврзан со возраста на детето и степенот на аваскуларните промени во предел на епифизата на главата на бутната коска при дијагностицирањето. Иако истражувањата на патологијата и патогенезата на болеста се вршат повеќе од сто години наназад, случаи на задоцнета, пропуштена или примарно погрешна дијагноза не се исклучок. Тоа ни дава за цел секогаш да правиме компарација на основните класификациони системи кои се користат за дијагностика при болеста на Legg-Calve-Pertes (LCP), опишани во текот на годините, да направиме проценка на нивната информативност во однос на степенот на настанатата деформација на главата на бутната коска и ацетабуларната празнина, како и при предвидување на крајните резултати.

По завршувањето на епидемиолошката студија за јувенилната остеонекроза на главата на бутната коска (болеста

на Legg-Calve-Perthes) во Република Македонија, за периодот 2000-2010 година, се направи компарацијата на резултатите добиени со нашата студија со резултатите кои што се објавени од страна на поголем број на земји.

КЛУЧНИ ЗБОРОВИ: Јувенилните остеохондрози, Болеста на Legg-Calve-Perthes (LCPB), конзервативен третман, класификации

ВОВЕД

Јувенилните остеохондрози претставуваат идиопатски, развојни пореметувања настанати како резултат на присутните циркулаторни нарушувања и последична појава на аваскуларна (асептична) некроза и пореметување на енхондралната осификација (хондогенеза и остеогенеза)во предел на примарните и секундарните јадра на осификацијата на зглобот.

Најчесто вклучени примарни јадра на осификацијата на:

- навикуларната коска на тарзусот (болеста на Kohler)
- лунарната коска (Keinbocks)
- прешленското тело (Calve)

Најчесто вклучени секундарни јадра на осификацијата на:

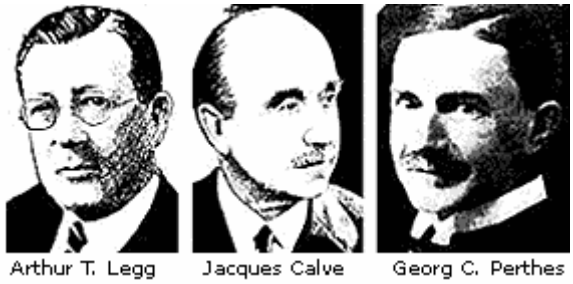
- апофизата и епифизата на цапителлум радии (Panner)
- главата на II-та метатарзална коска (Freiberg)
- скафоидната коска (Preisier)
- епифизата на главата на феморалната коска (Legg-Calve-Perthes)

Legg-Calve-Perthes (LCPB) претставува примарен остеохондритис на колкот, болест со се уште непозната етиологија.

Човекот кој што за прв пат во 1897 година ја опишал болеста е Karel Majdl (1853 - 1903) чешки хирург и професор на Чешкиот универзитет во Прага.

Личностите кои што се поврзуваат со името на болеста:

- Arthur Legg (1909, Boston, САД) ја опишал болеста како атипичен туберкулозен кокситисч
- Jasques Calve (1909, 1910, Berck Sur Mer, Франција) заедно со својот студент Paul Sourdat со употреба на нова машина за X зраци, опишале случаи на атипични промени на главата на феморалната коска кај децач
- Georg Perthes (1910, Tubingen, Германија) опишал случаи на “arthritis deformans juvenilis”
- Henning Waldenstorm (1908, Stockholm, шведска) прв ги опишал радиографските карактеристики на болеста, верувајќи дека се работи за туберкулозен процес и болеста ја означува како соха plana
- Phemister (1927) прв ја опишува патологијата на болеста како некроза на коската



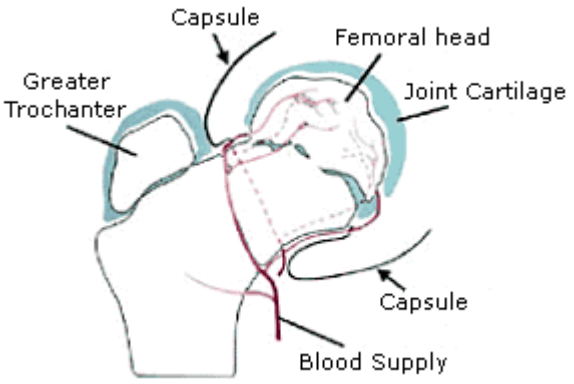
ЕТИОЛОГИЈА

Legg-Calve-Perthes претставува примарен остеохондритис на колкот, болест чија што точна етиологија е се уште непозната иако се доведува во врска со идиопатска аваскуларна некроза на епифизата на главата (или дел од главата) на феморалната коска како резултат на:

- прерано затварање на артеријата кој што го снабдува со крв ligamentum teres femoris не дозволувајќи на време да го прифати крвоснабдувањето a. circumflexa posterior
- намален број и волумен на анастомозите на a. circumflexa posterior во предел на епифизата и метафизата на феморалната коска што во корелација со зголемената физичка активност (со тоа и зголемена потреба за крвоснабдување) и оптеретување во предел на зглобот на колкот доведувааат до намалување на крвотокотч
- тромобоза на a. circumflexa;
- траума на зглобот на колкот
- воспаление (синовитис) на зглобот на колкот со подолготрајно зголемување на интраартикуларниот притисок во предел на

зглобот на колкот

- повторувачки исхемични инсулти во предел на главата на феморалната коска



За етиологијата на болеста на Legg-Calve-Perthes е познато дека:

- се јавува помеѓу 2 и 12 година од животот (најчесто помеѓу 4 и 8 година)
- се јавува со инциденца од 1:13000ч
- 4-6 пати е почеста појавата на оваа болест кај машките деца
- кај 10-20 % од случаите зафатени се двата колкови
- кај 10 % од случаите има наследност
- најчесто е зафатен предно-латералниот сегмент на феморалното јадро

КЛИНИЧКА СЛИКА

Болеста се јавува кај здрави, вообичаено активни деца со појава на болка (со различен интензитет и времетраење) во предел на колкот (ингвиналната регија), внатрешната страна на надколеницата се до коленото и постепен развој на истата, пратена со ограничена абдукција и внатрешна ротација на колкот (присутна аддукциона контрактура пратена со повемена флексорна контрактура на зглобот на колкот); нагласено накривување на детето.

ПАТОГЕНЕЗА

Снабдувањето со потребната крв на главата на феморалната коска се одвива преку три главни крвни садови:

крвните садови на метафизата

крвните садови на латералната епифиза

ограничено снабдување со крв од крвните садови на liggamentum teres

Снабдувањето со крв на главата на феморалната коска преку крвните садови на метафизата постепено се намалува на возраст од 4 (четири) години, а крвните садови на liggamentum teres не се добро развиени се до 7 (седум) годишна возраст така што меѓу возраста од 4 до 8 години крвоснабдувањето на епифизата на феморалната коска зависи исклучиво од arteria retinaculum ascendens која што е подложна на одредена форма на "надворешен" притисок било како резултат на оклузија на arteria retinaculum ascendens, зголемен интракапсуларен притисок, интраепифизарна тромбоза, васкуларни нарушувања или зголемена васкуларна исхемија на феморалната коска.

СТЕПЕНИ НА ПАТОЛОШКИТЕ ПРОМЕНИ

Дијагнозата на болеста на Legg-Calve-Perthes со примена на РТГ дијагностика (АП снимка на карлицата и аксијална слика на карлицата по Lauenstein во frog-leg позиција) се потврдува 3-4 месеци по појавата на клиничката симптоматологија.

При тоа со оглед на карактеристичните РТГ промени на главата на феморалната коска и интраартикуларниот простор на зглобот на колкот се разликуваат 4 (четири) фази на развој на болеста:

1 ФАЗА (ИСХЕМИЈА или НЕКРОЗА):

2 ФАЗА (ФАЗА НА ФРАГМЕНТАЦИЈА или РЕСОРПЦИЈА):

3 ФАЗА (ФАЗА НА РЕОСИФИКАЦИЈА):

4 ФАЗА (ФАЗА НА РЕМОДЕЛАЦИЈА):

5 ФАЗА (ФАЗА НА ОПОРАВУВАЊЕ):

ДИЈАГНОЗА

За одредување на болеста потребни се одредени испитувања:

КЛИНИЧКИ

Catterral-ов знак- ограничена надворешна ротација и флексија на колкот

болка во предел на колкот и внатрешната страна на надколеницата се до коленото

Duchenn-ов знак - накривување на болната нога

Намалување на движењата во предел на колкот (абдукција и внатрешна ротација)

Thomas-ов знак- умерена контрактура при флексија на колкот

Trendelenburg тестот е позитивен

Хипотрофија на мускулатурата на надколеницата

СЦИНТИГРАФИЈА НА ЗГЛОБОТ НА КОЛКОТ

КТ НА ЗГЛОБОТ НА КОЛКОТ

МРИ НА ЗГЛОБОТ НА КОЛКОТ

ЕХОТОМОГРАФИЈА НА ЗГЛОБОТ НА КОЛКОТ

АРТРОГРАФИЈА НА ЗГЛОБОТ НА КОЛКОТ

АНГИОГРАФИЈА НА ЗГЛОБОТ НА КОЛКОТ

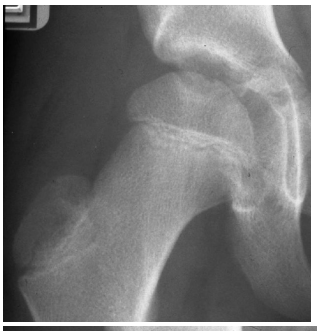
РТГ ДИЈАГНОСТИКА

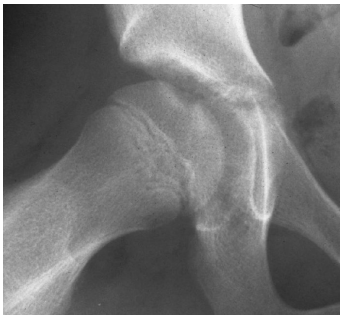
КЛАСИФИКАЦИИ:

1. CATTERRAL-ОВА КЛАСИФИКАЦИЈА

I СТЕПЕН

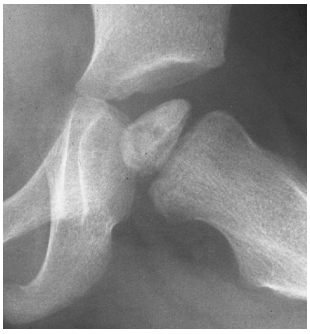
антеро-медијалниот сегмент на главата на феморалната коска е зафатен, без колапс на главата





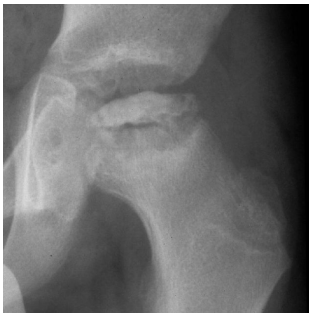
II СТЕПЕН

(латерален столб на глава на феморална коска не е зафатен)



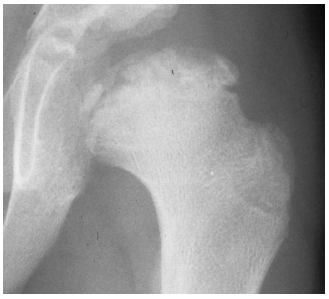
III СТЕПЕН

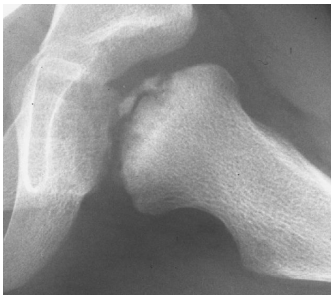
(латерален столб на глава на феморална коска е зафатен)



IV СТЕПЕН

(целата глава на феморална коска е зафатена)





2. SALTER-THOMPSON-ОВА КЛАСИФИКАЦИЈА

СТЕПЕН А

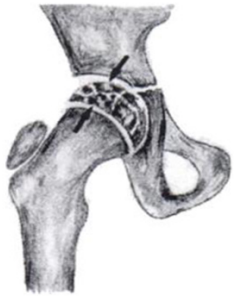
латерален столб на глава на феморална коска е присутен

СТЕПЕН Б

латерален столб на глава на феморална коска не е присутен

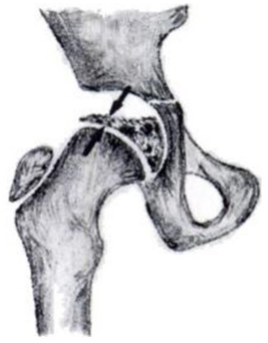
3. HERRING-ОВА (LATERAL PILLAR) КЛАСИФИКАЦИЈА

А. висината на латералниот столб (латерална 1/3) на главата на феморалната коска е со нормална морфологија и анатомија (фрагментација се случува во централен дел на главата на феморалната коска)



Б. висината на латералниот столб на главата е намален до 50 % од контралатералниот столб

В. висината на латералниот столб на главата на феморалната коска е намален над 50%



4. STULBERG-ОВА КЛАСИФИКАЦИЈА

Системот за класификација на Stulberg се користи за идентификација на почетокот на дегенеративната болест на зглобот на колкот т.е. болеста на Legg-Calve-Perthes со цел да ја потврди Herring-овата (lateral pillar) класификација. Во овој систем во предвид се земаат одреден број на радиографски параметри (сферичноста на главата на феморалната коска, должината на вратот на феморалната коска, поставеноста на ацетабуларната празнина и присуството на соха magna).

МЕТОДОЛОГИЈА НА ИСТРАЖУВАЊЕТО

Студијата претставува ретроспективна студија, за чие реалиизрање се користени податоци од пациенти со дијагностициран јувенилен остеохондрит, третирани во "Св. Еразмо"– специјална болница за ортопедија и трауматологија во Охрид во периодот од 2000 до 2010 година.

Истражувачката популација е дефинирана како деца на возраст од 2 до 14 години, со работна дијагноза primaren osteohondritis na kolkot, односно болеста на Legg-Calve-Perthes (LCPB).

Големината на примерокот, односно контингентот на испитаници ќе го сочинуваат 56 пациенти со примарен остеохондритис на колкот.

РЕЗУЛТАТИ

Резултатите на оваа студија во лекувањето на дел од пациентите заболени од примарен остеохондритис на колкот, односно болеста на Legg-Calve-Perthes (LCPB) во Р. Македонија во периодот од 2000 до 2010 година, укажуваат на нејзината застапеност во однос на одредените класификациони групи, демографските и биомедицинските карактеристики, хередитетот и нејзината прогресија.

Во истражувањето беа вклучени и анализирани 56 испитаници, половата структура на испитаниците ја сочинуваа 37 (66.07%) машки пациенти и 18 (32.14%) женски пациенти.

Пациентите беа на возраст од 2 до 14 години, со дијагностициран јувенилен остеохондрит на главата на бутната коска (болест на Legg-Calve-Perthes).

Возраста на испитаниците ја анализиравме во три возрасни групи: група од 14 (25%) пациенти помлади од

6 години, група од 36 (64.28%) пациенти на возраст од 6 до 9 години и група од 6 (10.71%) пациенти постари од 9 години.

Во однос на местото на живеење, резултатите презентираат дека мнозинството пациенти беа од урбана средина (71.43% наспроти 28.57%).

Дистрибуцијата на телесната тежина на заболените деца беше следната: 14 (25%) деца имаа ниска телесна тежина, 31 (55.36%) беа со нормална телесна тежина, најмал број и процент имаа зголемена телесна тежина, односно 11 (19.64%).

Според резултатите на FAS скалата, повеќе од половина испитаници, односно 31 (55.36%) имаа средна материјална состојба.

ЛЕКУВАЊЕ И ТРЕТМАН

Кај деца кои што се помали од 6-7 години, се препорачува опсервација и движење со патерици, ограничено трчање и скокање и медикаментозна терапија (ако е потребно).

1. КОНЗЕРВАТИВНО

Медикаментозна терапија (аналгетици или антиреуматици, не подолго од неколку дена)

Намалување на физичка активност, избегнување на трчање, скокање и спорт

Физикална терапија

ако е присутна вкочанетост на зглобот на колкот, мускулите и лигаментите кои што се во неговата околина и учествуваат ви формирање на зглобот на колкот се скратени. Вежби за истегнување ќе го одржат зглобот на колкот поподвижен и главата на феморалната коска во ацетабуларната празнина

Користење на патерици, одалка или количка

во дадена ситуација и положба детето има потреба да се пренесе тежината на телото на колкот кој што е зафатен, поради што со користење на патерици истиот ќе го заштити од дополнително оптеретување.

Тракција

ако кај детето е присутна силна болка во зглобот на колкот, периодот на мирување во кревет и тракција на заболената нога (постојано и умерено влечење на ногата) значително ќе ја намали болката.

Гипс

со цел да се задржи главата на феморалната коска во ацетабуларната празнина се препорачува специјален тип на гипсена имобилизација (Petri-ев гипс) која што ги движи нозете во раширена положба во време од 4 до 6 недели. Потоа се препорачува имобилизација само навечер како би се задржала подвижноста на зглобот на колкот со дневните активности на детето.

2. ОПЕРАТИВНО

Најголем број на опертивни третмани кај болеста на Legg-Calve-Perthes се во насока да на подобрување на облик на зглобот на колкот како би се спречила појава на зглобен артритис во текот на животот.

Олабавување на контрактурата

Децата кај кои што е присутна болеста на Legg-Calve-Perthes најчесто ја држат ногата скрстена врз телото. Оваа положба е прдизвикана од скаратувањето на околните мускули (аддуктори) и лигаменти, при што скратувањето е причина за влечење на главата на феморалната коска нагоре (контрактура).

Корекција на зглобот (realignment)

Кај деца постари од 6-8 години, корективната остеотомија е потребна како би се вратила нормалната сферичност на главата и формата на зглобот на колкот. Ова вклучува реориентација и корективната остеотомија на феморалната коска или карлицата (ацетабуларната празнина) и задржување на корегираната положба и растење на главата на феморалната коска со нормална форма, со користење на остеосинтетски материјал се додека трае лекувањето.

Отстрануавање на вишокот на коска и слободни коскени тела

Кај постарите деца кај кои што е присутна болка пратена со ограничени движења во предел на зглобот на колкот, со отстранување на вишокот на коска и слободни коскени тела околу главата на феморалната коска или репарација на оштететна зглобна ‘рскавица може да се олесни движење и намали болката.

Замена на зглобот на колкот

Кај децата кај кои што е присутна болеста на Legg-Calve-Perthes понекогаш имаат потреба од замена на зглобот на колкот подоцна во текот на животот. Овие операции може да се покомплицирани поради поголемиот ризик од фрактури на феморалната коска и оштетување на нервите.

3. НОВИ ТРЕТМАНИ

Важно е да се напомене дека новите третмани нудат потенцијална корист за подобрување на залекувањето на феморалната коска, но мора да се напомене дека истите не се испитани во иста мера како и конвенционалните третмани.

hip arthrodiastasis (дистракција на зглобот на колкот)

Пинови, времено поставени низ кожата во карлицата и феморалната коска со цел да се зголеми просторот мечу главата на феморалната коска и ацетабуларната празнина

Multiple epiphyseal drilling

Femoral neck tunneling

Core decompresion

методи кои што доведуваат до намалување на притисокот во внатрешноста на главата на феморалната коска и создавање на потенцијал за ново крвоснабдување

Bone marrow aspirate concentrate (BMAC)

вклучува земање на коскена срцевина на детето, деплазмирање и инјектирање во главата на феморалната коска.

Bisphosphonates

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Profesional paper

‘‘ИНЦИДЕНЦА И ХИРУРШКИ ТРЕТМАН НА ХОЛЕЛИТИЈАЗА ВО ОПШТА БОЛНИЦА КУМАНОВО ВО 2025’’

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АБСТРАКТ

Вовед: Холелитијаза е хронична хепатобилијарна болест поврзана со нарушен метаболизам на холестерол, билирубин и жолчни киселини, што доведува до формирање на жолчни камења. Почеста е кај жени и кај лица над 40 години. Најчеста клиничка манифестација е билијарната колика. Ултразвукот е златен стандард за дијагноза, додека лапароскопската холецистектомија е метод на избор.

Материјал и методи: Проспективна студија спроведена на Хируршкото одделение во Општа болница Куманово во периодот јануари–декември 2025 година, која опфати 165 пациенти со калкулозен холецистит. Анализирани беа демографските карактеристики, клиничките манифестации, ултразвучните наоди, видот на оперативниот третман и постоперативните исходи.

Резултати: Од вкупно 165 пациенти, 132 (80%) имале акутен, а 33 (20%) хроничен калкулозен холецистит. Лапароскопска холецистектомија беше изведена кај 156 (94,5%) пациенти, со конверзија кај 6 (3,6%), додека 3 (1,8%) беа оперирани со отворен пристап. Жените доминираа (67%), а 56% беа над 40 години. Најчести симптоми беа абдоминална болка (100%), диспепсија (79%), наузеа (73%) и повраќање (67%). Мултипли калкулуси беа присутни кај 68% од пациентите. Повеќето пациенти (91%) беа отпуштени првиот постоперативен ден. Постоперативни компликации се регистрирани кај 14 (8,5%) пациенти. Од нив, крвавење не е забележано кај ниту еден пациент, умбиликална хернија е регистрирана кај 3 пациенти, истекување на жолчка кај 1 пациент, додека постхолецистектомиски синдром е евидентиран кај 10 пациенти.

Дискусија: Холелитијазата е честа болест со типична клиничка слика на билијарна колика. Дијагнозата се поставува со анамнеза, клинички и ултразвучен преглед. Лапароскопската холецистектомија претставува безбеден и ефикасен третман со ниска стапка на компликации и овозможува рано отпуштање. Нашите резултати ја потврдуваат како метод на избор во современата хируршка практика.

Клучни зборови: холелитијаза, калкулозен холецистит, лапароскопска холецистектомија, билијарна колика, ултразвук

ВОВЕД

Холелитијазата (Cholelithiasis) претставува присуство на конкременти (каменчиња) во жолчното ќесе или жолчните патишта. Холелитијаза е хронична, рекурентна хепатобилијарна болест, чија основа е нарушен метаболизам на холестерол, билирубин и жолчни киселини, што се карактеризира со формирање на жолчни камења во хепаталните жолчни канали или жолчното ќесе. (1)

Се смета за значаен јавно-здравствен проблем поради високата зачестеност и честата потреба од хируршки третман. Заболувањето е почесто кај жените, со

однос жена:маж од приближно 2–3:1, што најчесто се објаснува со влијанието на естрогените врз метаболизмот на холестеролот. Исто така, ризикот за појава на болеста се зголемува со возраста, при што најчесто се дијагностицира кај лица постари од 40 години. (2)

Постојат три основни видови камења во жолчното ќесе: холестеролски камења, кои се најчести и се состојат главно од холестерол; пигментни камења, кои содржат главно билирубин и калциум и обично се потемни; и мешани камења, кои имаат комбинација од холестерол, билирубин и минерални соли. (3)

Главни ризикфактори за развој на холелитијаза вклучуваат обезитет (поради зголемена секреција на холестерол и суператаурација на жолчката), брза редукција на телесна тежина (што го нарушува нормалното празнење на жолчното ќесе), дијабетес, други метаболички нарушувања, генетска предиспозиција, заболувања на црниот дроб и одредени медикаменти кои влијаат на функцијата на жолчното ќесе или метаболизмот на жолчката. (4)

Клиничката слика кај холелитијаза може значително да варира – од потполно асимптоматска форма, која се открива случајно при ултразвучен преглед, до тешки и потенцијално опасни состојби. Најчеста манифестација е билијарната колика, која се карактеризира со силна болка во десниот горен квадрант или епигастриум, која често се шири кон грбот и десното рамо и може да биде придружена со гадење и повраќање. Болките обично се јавуваат во вид на напади со траење од 30 минути до неколку часа, најчесто после масни или обилни оброци. (3,5)

Освен тоа, може да се појават подуеност, диспепсија и блага фебрилност. Пожолтување на кожата и лигавиците може да укажува на опструкција на жолчните канали. Кога болката трае повеќе од 12 часа или е придружена со повишена температура и/или пожолтување, ова е сомнително за појава на компликации како акутен холециститис, холангитис или панкреатитис, што бара итна медицинска проценка и третман. (6)

Дијагнозата на холелитијаза најчесто се поставува со ултразвучен преглед на абдомен, кој претставува златен стандард поради неговата широка достапност и висока дијагностичка точност. (7)

Во одредени случаеви, особено при сомневање на опструкција на заедничкиот жолчен канал или компликации, се применуваат дополнителни сликарски испитувања како компјутерска томографија (CT) и магнетна резонанца холангиопанкреатографија (MRCP), која е неинвазивен и прецизен метод за визуелизација на жолчните и панкреасните канали Ендоскопската ретроградна холангиопанкреатографија (ERCP) е дијагностички и терапевтски метод што може да овозможи и третман (на пр. отстранување на камења), но се користи почесто кога има висока веројатност за обструкција или кога интервенцијата е потребна. (8,9)

Лабораториските испитувања, вклучително зголемени воспалителни параметри и абнормални хепатални ензими, може да бидат индикативни за воспаление или опструкција на жолчниот тракт. (6)

Третманот на симптоматска холелитијаза е претежно хируршки. Лапароскопската холецистектомија се смета за метод на избор, бидејќи е помалку инвазивна, има пократко време на опоравување и помал ризик од постоперативни компликации. (10)

Отворената холецистектомија се резервира за пациенти со комплицирани случаи, како што се акутен холециститис со перфорација, камен во заедничкиот жолчен канал со обструкција, или кога лапароскопската процедура бара конверзија поради анатомски или технички пречки. (9, 10,11)

МАТРИЈАЛ И МЕТОДИ

Проспективна студија спроведена на Хируршкото одделение при Општа болница Куманово во периодот јануари–декември 2025 година, која опфати 165 пациенти со дијагноза калкулозен холецистит, со цел да се прикажат инциденцата, клиничкиот профил и видовите на оперативен третман на холелитијаза, како и постоперативните исходи. Пациентите беа анализирани според типот на болеста, полот, возраста, клиничките манифестации, должината на хоспитализација, ултразвучните наоди и постоперативните компликации.

РЕЗУЛТАТИ

Од вкупно 165 пациенти оперирани за калкулозен холецистит, 33 (20%) имале хроничен, а 132 (80%) акутен некомплициран калкулозен холецистит.

Лапароскопската холецистектомија била изведена кај 156 пациенти (94,5%), кај 6 пациенти (3,6%) била

направена конверзија во отворена операција, додека 3 пациенти (1,8%) биле оперирани со примарна отворена холецистектомија.

Според полот, 55 пациенти (33%) биле мажи, а 110 (67%) жени.

Според возраста, 72 пациенти (44%) биле на возраст до 40 години, додека 93 пациенти (56%) биле над 40 години.

Сите пациенти (100%) имале болка во горниот дел на абдоменот под десниот ребрен лак, додека дополнителни симптоми вклучувале диспепсија кај 130 пациенти (79%), наузеа кај 120 пациенти (73%), повраќање кај 110 пациенти (67%), жолтица кај 10 пациенти (6%) и треска кај 14 пациенти (8,5%).

Ултразвучниот преглед покажа солитарен калкулус кај 52 пациенти (32%), а мултипли калкулуси кај 113 пациенти (68%).

Од вкупно 165 пациенти, 120 (91%) биле отпуштени првиот постоперативен ден, 36 пациенти (27%) биле отпуштени подоцна од 1 ден, додека 9 пациенти биле отпуштени по 5–7 дена.

Постоперативни компликации се регистрирани кај 14 (8,5%) пациенти. Од нив, крвавење не е забележано кај ниту еден пациент, умбиликална хернија е регистрирана кај 3 пациенти, истекување на жолчка кај 1 пациент, додека постхолецистектомиски синдром е евидентиран кај 10 пациенти.

ДИСКУСИЈА

Холелитијазата е заболување чија инциденца во светски рамки изнесува 10–20% од возрасната популација и е почеста кај женскиот пол. Типична клиничка манифестација е билијарната (жолчната) колика, која се карактеризира со силна болка во епигастриумот или десниот хипохондриум, со ирадијација кон грбот или десното рамо. Чести придружни симптоми се слабост, гадење, повраќање и неможност да се најде соодветна положба на телото. (12)

Дијагнозата се поставува врз основа на правилно земена анамнеза, физикален преглед, лабораториски анализи и ултразвучен преглед како метода на избор. Пациентите со асимптоматска калкулоза на билијарниот систем не бараат третман поради бенигниот тек на болеста. Пациентите со повторувачки епизоди на билијарна колика треба да се оперираат во рок од неколку месеци, додека кај оние со изразени симптоми е индициран поитен хируршки третман. (13)

Лапароскопската холецистектомија претставува безбедна и ефикасна метода за третман на калкулозен холецистит, со ниска стапка на сериозни постоперативни компликации и можност за рано отпуштање на пациентите, особено кај некомплицираните форми. Резултатите од нашата студија покажуваат дека пациентите со акутен некомплициран холецистит можат да бидат отпуштени веќе првиот постоперативен ден, што ја намалува должината на хоспитализација и интрахоспиталните инфекции. (14)

Во нашата установа, Хируршкото одделение при Општа болница Куманово, лапароскопската холецистектомија најчесто се применува како оперативен метод за третман на холелитијаза, со ниска стапка на постоперативни компликации. Овие податоци дополнително ја потврдуваат лапароскопската холецистектомија како метод на избор за третман на калкулозен холецистит во современата хирургија.

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Profesional paper

ВЛИЈАНИЕ НА HPV ВАКЦИНАЦИЈАТА ВРЗ ТОВАРОТ ОД КАРЦИНОМОТ НА ГРЛОТО НА МАТКАТА ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА: ЕПИДЕМИОЛОШКА АНАЛИЗА ЗА ПЕРИОДОТ 2009–2026 ГОДИНА

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АПСТРАКТ

Вовед: Карциномот на грлото на матката претставува една од ретките малигни неоплазми што може во голема мера да се превенира преку примарна превенција (HPV вакцинација) и секундарна превенција (организиран скрининг). Воведувањето на HPV вакцинацијата во националните програми за имунизација доведе до значително намалување на HPV инфекциите, високостепените цервикални интраепителни неоплазии и инциденцата на инвазивниот карцином во повеќе земји со висок вакцинален опфат.

Цел: Да се анализираат достапните официјални епидемиолошки податоци за карциномот на грлото на матката и HPV вакцинацијата во Република Северна Македонија во периодот 2009–2026 година и да се споредат со трендовите во земјите од Балканот, Европа и светот.

Материјал и методи: Спроведена е ретроспективна дескриптивна и компаративна епидемиолошка анализа базирана на официјално достапни податоци од Светската здравствена организација (WHO), Меѓународната агенција за истражување на ракот (IARC/GLOBOCAN), ICO HPV Information Centre, Европскиот центар за превенција и контрола на болести (ECDC), Институтот за јавно здравје и Министерството за здравство на Република Северна Македонија.

Резултати: Анализата покажува дека Република Северна Македонија воспоставила национална програма за HPV вакцинација во 2009 година и постепено ги усогласува превентивните активности со препораките на WHO. И покрај тоа, товарот од карциномот на грлото на матката останува значителен. Според достапните официјални податоци, стандардизираната инциденца изнесува приближно 7,5 случаи на 100.000 жени, а морталитетот останува релативно висок во однос на земјите со долгогодишен висок вакцинален опфат. Компаративната анализа покажува дека државите со вакцинален опфат над 80–90% бележат значително побрзо намалување на инциденцата и преканцерозните лезии.

Заклучок: Република Северна Македонија има воспоставено добра основа за долгорочно намалување на товарот од карциномот на грлото на матката. Понатамошното зголемување на вакциналниот опфат, организираниот HPV-базиран скрининг и континуираното епидемиолошко следење претставуваат клучни предуслови за достигнување на целите на глобалната стратегија на WHO за елиминација на ова заболување како јавно-здравствен проблем.

Клучни зборови: HPV, карцином на грлото на матката, вакцинација, епидемиологија, Република Северна Македонија.

ВОВЕД

Карциномот на грлото на матката претставува четврта најчеста малигна неоплазма кај жените во светот и една од водечките причини за смртност од малигни заболувања кај женската популација во земјите со ниски и средни приходи. Според проценките на Меѓународната агенција за истражување на ракот (IARC), секоја година се регистрираат повеќе од 660.000 нови случаи и над 350.000 смртни исходи на глобално ниво. Овие бројки укажуваат дека, и покрај постоењето на ефикасни превентивни мерки, карциномот на грлото на матката останува значаен јавно-здравствен предизвик.

Перзистентната инфекција со високо-ризични типови на хуман папилома вирус (HPV), особено типовите 16 и 18, претставува неопходен етиолошки фактор за развој на повеќе од 95% од случаите на карцином на грлото на матката. Покрај овие типови, значајна улога имаат и HPV 31, 33, 45, 52 и 58, кои се опфатени со современата деветвалентна вакцина. Развојот на профилактичките HPV вакцини претставува една од најзначајните достигнувања во современата превентивна медицина. Голем број рандомизирани клинички студии и национални програми покажаа дека вакцинацијата значително ја намалува зачестеноста на перзистентните HPV инфекции, високостепените цервикални интраепителни неоплазии (CIN2+ и CIN3+) и инвазивниот карцином на грлото на матката. Во 2020 година Светската здравствена организација ја усвои Глобалната стратегија за елиминација на карциномот на грлото на матката, поставувајќи ги целите 90–70–90 до 2030 година:

најмалку 90% од девојчињата да бидат целосно вакцинирани против HPV до 15-годишна возраст;

најмалку 70% од жените да бидат скринирани со високо чувствителен тест до 35 и повторно до 45 години;

најмалку 90% од жените со преканцерозни лезии или инвазивен карцином да добијат навремено лекување.

Република Северна Македонија ја воведе HPV вакцинацијата во националниот календар за имунизација во 2009 година, со што се приклучи кон европските стратегии за примарна превенција на карциномот на грлото на матката. Сепак, достапните податоци покажуваат дека вакциналниот опфат и понатаму варира меѓу генерациите, а потребно е дополнително унапредување на организираниот скрининг и континуираното епидемиолошко следење.

Во Република Северна Македонија, вакцинацијата против хуман папилома вирус (HPV) кај момчињата официјално беше воведена во Националниот календар за редовна имунизација во 2024 година, со премин на деветвалентната вакцина (Gardasil 9). Вакцинацијата започна во мај 2024 година и опфаќа рутинска имунизација на 12-годишни момчиња, како и дополнителна („catch-up“) вакцинација на момчиња до 18-годишна возраст. Оваа мерка има за цел да ја намали циркулацијата на високоризичните HPV типови, да обезбеди директна заштита од HPV-асоцирани малигнитети кај машката популација и да придонесе кон создавање на колективен имунитет.

МАТЕРИЈАЛ И МЕТОДИ

Ова истражување претставува ретроспективна, дескриптивна и компаративна епидемиолошка студија, насочена кон проценка на влијанието на воведувањето на вакцинацијата против хуманиот папилома вирус (HPV) врз епидемиолошките карактеристики на карциномот на грлото на матката во Република Северна Македонија во периодот 2009–2026 година. Истражувањето е базирано на анализа на официјално достапни секундарни податоци и не вклучува индивидуални медицински податоци, поради што не беше потребна дополнителна согласност од испитаници. За подготовка на анализата беа користени официјални податоци и публикации од следните институции:

Светска здравствена организација (WHO);

Меѓународна агенција за истражување на ракот (IARC);

GLOBOCAN;

ICO/IARC HPV Information Centre;

Европски центар за превенција и контрола на болести (ECDC);

Институт за јавно здравје на Република Северна Македонија;

Министерство за здравство на Република Северна Македонија;

Национален регистар за малигни неоплазми;

рецензирани научни публикации индексирани во PubMed, Scopus и Web of Science.

Во анализата беа вклучени најновите достапни официјални извештаи и научни публикации објавени

до 2026 година. Истражувањето ги опфаќа следните показатели:

инциденца на карциномот на грлото на матката;

морталитет;

возраста-стандардизирани стапки (ASR);

вакцинален опфат против HPV;

трендови на организиран скрининг;

споредба со земјите од Западен Балкан;

споредба со Европската Унија;

споредба со земји со високо успешни програми за елиминација (Австралија, Шведска и Обединетото Кралство).

Податоците беа обработени со примена на дескриптивни статистички методи. Континуираните варијабли се прикажани како апсолутни вредности, проценти и стандардизирани стапки на 100.000 жители, согласно методологијата на IARC и WHO. Компаративната анализа се базираше на:

споредба на официјални стапки;

анализа на временските трендови;

споредба на националните програми за вакцинација;

анализа на исполнувањето на индикаторите на WHO 90–70–90.

Поради ограничената достапност на континуирани национални годишни податоци за целиот период 2009–2026 година, не беа применети Joinpoint регресија, APC/AAPC анализи или други модели за процена на временски трендови. Овој пристап е во согласност со принципите на научната методологија, со цел да не се изведуваат статистички заклучоци врз основа на непотполни серии на податоци. Истражувањето користи исклучиво јавно достапни агрегирани податоци и не обработува лични или чувствителни здравствени информации. Согласно националните и меѓународните етички препораки за секундарна анализа на јавно достапни податоци, не беше потребно одобрување од етичка комисија.

РЕЗУЛТАТИ

Карциномот на грлото на матката и понатаму претставува едно од најзначајните малигни заболувања кај женската популација во Република Северна Македонија. Иако во последната деценија се бележи подобрување на превентивните активности преку воведување на HPV вакцинацијата и организирани програми за скрининг, товарот од болеста останува повисок во споредба со повеќето земји од Европската Унија. Според официјалните податоци на Светската здравствена организација и ICO/IARC HPV Information Centre, во Република Северна Македонија годишно се регистрираат приближно 113–150 нови случаи на карцином на грлото на матката, додека бројот на смртни случаи се движи меѓу 62 и 68 годишно. Возраста-стандардизираната инциденца изнесува 7,5 случаи на 100.000 жени, а суровата инциденца 10,9 случаи на 100.000 жени. Кумулативниот ризик за развој на карцином до 74-годишна возраст е 0,8 %, додека односот морталитет/инциденца изнесува 0,55, што укажува дека товарот од ова заболување останува значаен јавно-здравствен проблем во земјата.

Индикатор	Вредност	Извор
Нови случаи годишно (проценка)	113	ICO/IARC HPV Information Centre
Просечен годишен број на случаи	≈113–150	ICO/IARC, Министерство за здравство
Смртни случаи годишно	62–68	WHO / ICO-IARC
Возрасно стандардизирана инциденца (ASR)	7,5/100.000	WHO
Сурова инциденца	10,9/100.000	WHO
Кумулативен ризик до 74 години	0,8 %	WHO
Однос морталитет/инциденца	0,55	WHO
Национален регистар за малигни неоплазми	Да	WHO
Национална HPV вакцинација	Да	WHO
Година на воведување	2009	WHO
Целна возраст	12 години	WHO
Опфат со прва доза (2020)	45 %	WHO
Комплетна вакцинација (2020)	30 %	WHO

Табела 1. Официјални показатели за карциномот на грлото на матката во Република Северна Македонија

Националната програма за HPV вакцинација беше воведена во 2009 година како дел од редовниот календар за имунизација. Во текот на анализираниот период се забележуваат значителни промени во организацијата на програмата, достапноста на вакцините, стратегиите за информирање на јавноста и опфатот на целните групи. Во почетните години програмата се соочуваше со ограничен вакцинален опфат, што беше поврзано со недоволна информираност на населението, резервираност кон новата вакцина и логистички предизвици. Во поновите години се забележува

постепено подобрување на организацијата, зголемена едукација на родителите и здравствените работници и поголема достапност на вакцината. Резултатите укажуваат дека висок и континуиран вакцинален опфат е предуслов за значително намалување на товарот од HPV-асоцираните заболувања во наредните децении. Воведувањето на HPV вакцинацијата во Република Северна Македонија во 2009 година претставуваше значаен исчекор во примарната превенција на карциномот на грлото на матката. Во текот на анализираниот период програмата помина низ неколку фази на развој, кои се карактеризираат со организациски промени, унапредување на логистиката, подобрување на достапноста на вакцините и постепено зголемување на јавната информираност. Во првите години од имплементацијата, вакциналниот опфат беше ограничен поради недоволна информираност, резервираност на дел од родителите и недоволно развиени комуникациски стратегии. Во следните години се забележува постепено подобрување на организацијата на имунизацијата, воведување на дополнителни едукативни активности и поголема вклученост на примарната здравствена заштита. Особено значајно е што националната програма постепено се усогласуваше со препораките на Светската здравствена организација и Европскиот центар за превенција и контрола на болести, што создаде услови за подобрување на долгорочната превенција.

Период	Главни карактеристики
2009–2012	Воведување на вакцинацијата во редовниот календар за имунизација
2013–2016	Подобрување на организацијата и достапноста на вакцините
2017–2019	Интензивирање на здравствената едукација и промотивните активности
2020–2022	Одржување на програмата во услови на COVID-19 пандемија
2023–2026	Усогласување со современите европски препораки и проширување на превентивните активности

Табела 2. Развој на националната HPV програма во Република Северна Македонија (2009–2026)

Компаративната анализа покажува значајни разлики помеѓу земјите од Балканот во однос на организацијата на HPV вакцинацијата, националниот скрининг и товарот од карциномот на грлото на матката. Словенија и Хрватска имаат најразвиени организирани програми за превенција, со високо ниво на интеграција помеѓу вакцинацијата и организираниот скрининг. Србија и Бугарија во последните години бележат напредок преку проширување на националните програми. Република Северна Македонија, Албанија и Косово се соочуваат со предизвици поврзани со нерамномерен вакцинален опфат, ограничени ресурси и потреба од дополнително јакнење на скрининг-програмите

Држава	Национална HPV програма	Организиран скрининг	Главен предизвик
Северна Македонија	Да	Во развој	Подобрување на вакциналниот опфат
Србија	Да	Делумно организиран	Регионални разлики
Хрватска	Да	Да	Одржување на висок опфат
Словенија	Да	Да	Континуирано подобрување
Бугарија	Да	Делумно организиран	Низок вакцинален опфат во одделни региони
Грција	Да	Да	Подобрување на опфатот кај адолесцентите
Албанија	Да	Ограничен	Развој на национален скрининг
Косово	Во развој	Ограничен	Проширување на превентивните програми

Табела 3. Споредба на националните HPV програми на земјите од Балканот

Во споредба со просекот на Европската Унија, Република Северна Македонија сè уште има повисок товар од карциномот на грлото на матката. Главните причини се:

понизок вакцинален опфат во споредба со земјите со долгорочно успешни програми;

ограничен организиран HPV-базиран скрининг;

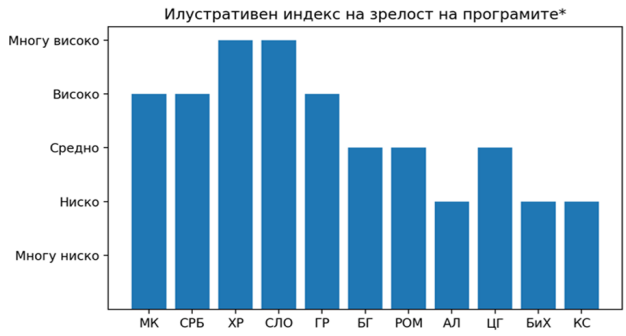
нерамномерна достапност на превентивните услуги;

различен степен на здравствена писменост во популацијата.

Од друга страна, воспоставувањето на национална програма за вакцинација и подобрувањето на системот за епидемиолошки надзор претставуваат значајна основа за понатамошно намалување на инциденцата.

Индикатор	Северна Македонија	Просек ЕУ
Национална HPV вакцинација	✔	✔
Организиран скрининг	Во развој	Во повеќето земји воспоставен
HPV ДНК тестирање	Постепено воведување	Широко достапно
Усогласеност со WHO 90–70–90	Делумна	Висока во повеќе земји

Табела 4. Компаративен приказ на превентивните програми



Графикон 10. Илустративен индекс на зрелост на националните програми за превенција на карциномот на грлото на матката во Република Северна Македонија и избрани земји од Балканот.

Столбестиот график прикажува компаративен, квалитативен индекс на зрелост на националните програми за HPV вакцинација и превенција на карциномот на грлото на матката. Проценката се темели на клучни компоненти на програмите, вклучувајќи ја имплементацијата на националната HPV вакцинација, воведувањето на деветвалентната вакцина, родово неутралната вакцинација, организираниот HPV-базиран скрининг, развиеноста на националните регистри и системите за епидемиолошки надзор, како и усогласеноста со препораките на Светската здравствена организација (WHO). Во илустративниот модел, Хрватска и Словенија се прикажани како земји со многу висока зрелост на програмите, додека Република Северна Македонија, Србија и Грција се прикажани со високо ниво на развиеност. Бугарија, Романија и Црна Гора се позиционирани во категоријата средно ниво, додека Албанија, Босна и Херцеговина и Косово се прикажани со пониско ниво на развиеност, што главно се должи на различниот степен на имплементација на родово неутралната вакцинација, организираниот скрининг и националните регистри.

Индикатор	Статус во Северна Македонија
HPV вакцинација до 15 години	Во напредок
Скрининг до 35 години	Делумно исполнет
Повторен скрининг до 45 години	Во развој
Навремено лекување	Континуирано подобрување

Табела 5. Исполнување на индикаторите на WHO

SWOT анализа на националната програма

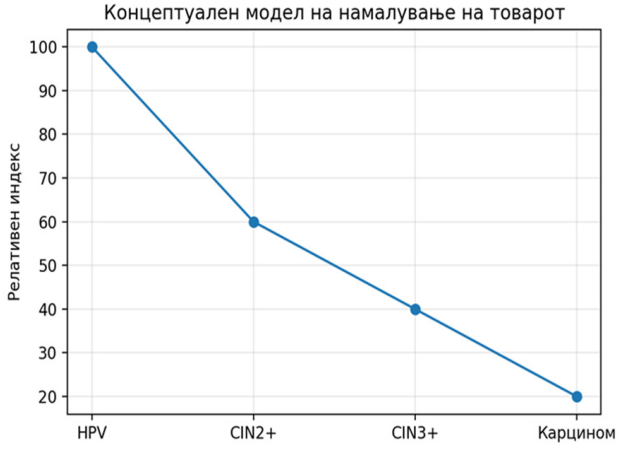
Силни страни	Слабости
Национална програма за HPV вакцинација	Недоволен вакцинален опфат во одделни генерации
Искусен кадар во јавното здравство	Нецелосен организиран HPV скрининг
Законска рамка	Ограничени финансиски ресурси
Можности	Закани
Усогласување со европските стандарди	Дезинформации за вакцините
Воведување HPV ДНК тестирање	Намален интерес за вакцинација
Подобра дигитална евиденција	Социјални и регионални нееднаквости

Табела 6. SWOT анализа

Резултатите од ова истражување укажуваат дека Република Северна Македонија во изминатите седумнаесет години воспостави стабилна институционална рамка за превенција на карциномот на грлото на матката. Воведувањето на HPV вакцинацијата, заедно со постепеното подобрување на скрининг-програмите, претставува значајна основа за намалување на идниот товар од болеста. Во исто време, компаративната анализа покажува дека земјите кои рано постигнале висок и стабилен вакцинален опфат, како Словенија и неколку западноевропски држави, веќе бележат значително намалување на преканцерозните лезии и инциденцата на инвазивниот карцином. Ова укажува дека и во Република Северна Македонија може да се очекува сличен тренд во наредните години, доколку се обезбеди континуирано висока покриеност со вакцинација, организиран HPV-базиран скрининг и редовно епидемиолошко следење.

Графикон 2. Тренд на опфатот со HPV вакцинација во Република Северна Македонија (2010–2026 година).

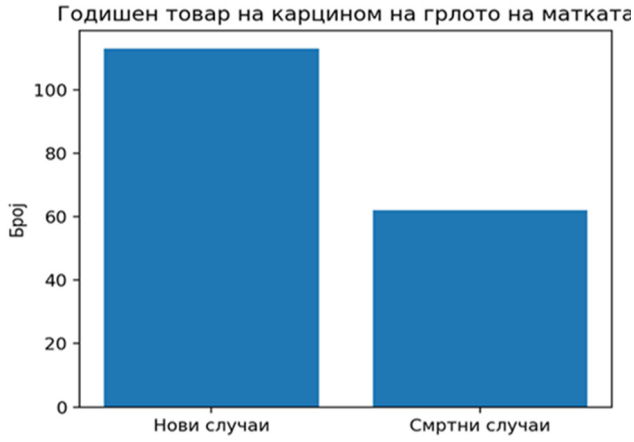
Линискиот график го прикажува трендот на вакциналниот опфат со HPV вакцинацијата во Република Северна Македонија во периодот 2010–2026 година. Прикажана е постепена тенденција на зголемување на опфатот, од приближно 20% во почетниот период до околу 55% во 2026 година. Најизразен пораст е забележан по 2021 година, што кореспондира со интензивирањето на промотивните активности, подобрувањето на достапноста на вакцините, воведувањето на деветвалентната HPV вакцина (Gardasil® 9) и проширувањето на бесплатната вакцинација и за момчиња во рамките на родово неутралната имунизација. Зголемувањето на вакциналниот опфат претставува еден од најважните индикатори за успешноста на националната програма за HPV вакцинација и создава предуслови за намалување на циркулацијата на високоризичните HPV генотипови, намалување на зачестеноста на високостепените цервикални интраепителни неоплазии (CIN2+ и CIN3+) и, на долг рок, намалување на инциденцата и морталитетот од карциномот на грлото на матката.



Графикон 3. Концептуален модел на намалување на товарот од HPV-поврзаните заболувања по имплементација на HPV вакцинацијата.

Во првите години од имплементацијата програмата беше насочена кон девојчињата од препорачаната возрасна група, а во следниот период континуирано се унапредуваше преку подобрување на логистиката, достапноста на вакцините и здравствената едукација. Значајна пресвртница претставува 2024 година, кога националната програма беше проширена со воведување на деветвалентната HPV вакцина и бесплатна вакцинација за момчиња и девојчиња до 19-годишна возраст. Со ова Република Северна Македонија се приклучи кон современиот европски концепт на родово неутрална HPV вакцинација, чија цел е намалување на циркулацијата на вирусот и обезбедување поширока популациска заштита. Иако програмата бележи континуиран организациски развој, достапните извештаи покажуваат дека вакциналниот опфат останува понизок од стратешката цел на Светската здравствена организација, според која најмалку 90% од девојчињата треба да бидат целосно вакцинирани до 15-годишна возраст. Линискиот график ја прикажува очекуваната постепена редукција на релативниот товар на заболувањата долж природниот тек на HPV-инфекцијата – од инфекција со хуман папилома вирус (HPV), преку високостепените цервикални интраепителни неоплазии (CIN2+ и CIN3+), до инвазивен карцином на грлото на матката. Прикажаниот концептуален модел ја илустрира високата ефикасност на HPV вакцинацијата во прекинување на прогресијата од перзистентна HPV инфекција кон преканцерозни лезии и инвазивен карцином. Намалувањето на релативниот индекс ја одразува очекуваната акумулација на превентивниот

ефект со текот на времето, при што најголемо намалување се очекува кај појавата на инвазивниот карцином. Ваквиот тренд е во согласност со резултатите од долгогодишните популациски студии, кои покажуваат значително намалување на инфекциите со високоризични HPV генотипови, инциденцата на CIN2+, CIN3+ и карциномот на грлото на матката кај популации со висок вакцинален опфат и организиран HPV-базиран скрининг.



Графикон 4. Годишен товар на карциномот на грлото на матката.

Споредбен приказ на профилактичките HPV вакцини според нивниот тип, опфатените HPV генотипови, годината на првото регулаторно одобрување и главните индикации за примена. Со развојот од бивалентната кон деветвалентната вакцина значително е проширен спектарот на заштита од високоризични и нискоризични HPV генотипови. Деветвалентната вакцина (Gardasil® 9) обезбедува најширока заштита и се смета за стандард во современите национални програми за имунизација, бидејќи покрива HPV генотипови одговорни за приближно 90% од случаите на карцином на грлото на матката, како и значителен дел од другите HPV-поврзани малигни заболувања и гениталните кондиломи. Столбестиот график го прикажува односот помеѓу бројот на новодијагностицирани случаи (инциденца) и бројот на смртни случаи (морталитет) од карцином на грлото на матката во текот на една година. Приказот ја илустрира значајната разлика помеѓу бројот на нови заболени и бројот на починати, нагласувајќи дека карциномот на грлото на матката сè уште претставува значителен јавно-здравствен товар. Односот помеѓу инциденцата и морталитетот е важен индикатор за ефикасноста на превентивните програми, раното откривање, достапноста на современата дијагностика и навременото лекување. Република Северна Македонија ја воведе HPV вакцинацијата во редовниот календар за имунизација во 2009 година, со што започна организирана примарна превенција на карциномот на грлото на матката.

ДИСКУСИЈА

Карциномот на грлото на матката претставува едно од ретките малигни заболувања кај кое е можно значително намалување на инциденцата и морталитетот преку комбинирана примена на примарна и секундарна превенција. Инфекцијата со високоризични типови на хуман папилома вирус (HPV) е неопходен етиолошки фактор за развојот на повеќе од 95% од случаите на ова заболување, што ја прави HPV вакцинацијата една од најефикасните интервенции во современото јавно здравје. Резултатите од нашата анализа покажуваат дека Република Северна Македонија направила значителен институционален напредок по воведувањето на националната програма за HPV вакцинација во 2009 година. Сепак, во споредба со земјите што рано постигнаа висок вакцинален опфат и организиран скрининг, товарот од карциномот на грлото на матката и понатаму останува релативно висок. Ова укажува дека воведувањето на вакцинацијата, иако претставува неопходен предуслов, не е доволно само по себе. Најдобри резултати се постигнуваат кога вакцинацијата се комбинира со организиран HPV-базиран скрининг, навремена дијагностика и ефикасен третман. Австралија е првата држава што се смета за реален кандидат за елиминација на карциномот на грлото на матката како јавно-здравствен проблем. Високиот вакцинален опфат, организираниот национален скрининг и широката примена на HPV ДНК тестирањето доведоа до драматично намалување на HPV инфекциите, аногениталните брадавици, високостепените цервикални интраепителни неоплазии и инвазивниот карцином. Австралиското искуство покажува дека континуитетот на програмата, а не само нејзиното воведување, е клучен за долгорочен успех. Слични резултати се забележуваат во Шведска, каде националниот регистар за вакцинација, интегрираниот скрининг и високата здравствена писменост овозможија значително намалување на инциденцата кај помладите генерации. Податоците од Обединетото Кралство покажуваат дека вакцинираните генерации имаат значително понизок

ризик за развој на цервикален карцином во споредба со невакцинираните кохорти, особено кога вакцинацијата е спроведена пред почетокот на сексуалната активност. Овие искуства потврдуваат дека долгорочниот ефект на HPV вакцинацијата се манифестира по повеќе години, што е во согласност со природниот тек на HPV инфекцијата и карциногенезата. Затоа, моменталниот товар од болеста во Северна Македонија не треба да се толкува како неуспех на програмата, туку како одраз на фактот дека целосниот ефект од вакцинацијата ќе биде видлив кај генерациите кои биле имунизирани во препорачаната возраст и кои допрва ќе влезат во периодот со најголем ризик за развој на инвазивен карцином. Во споредба со земјите од Западен Балкан, Република Северна Македонија се наоѓа во групата држави што воспоставиле национална програма за HPV вакцинација, но сè уште се соочуваат со предизвици во постигнувањето висок и рамномерно распределен вакцинален опфат. Словенија претставува пример за добро интегриран модел на вакцинација и организиран скрининг, додека Хрватска бележи постепено подобрување на опфатот преку засилени јавноздравствени кампањи. Србија и Бугарија, слично како Северна Македонија, работат на понатамошно унапредување на програмите и подобрување на достапноста на превентивните услуги. Овие разлики не се должат само на организацијата на здравствениот систем, туку и на социоекономските услови, нивото на здравствена писменост, довербата во вакцинацијата и континуитетот на превентивните политики. Земјите со стабилни национални регистри, добро развиени системи за повикување на скрининг и висока доверба во здравствените институции генерално бележат подобри резултати. Наодите од ова истражување имаат значајни импликации за националната здравствена политика. Прво, неопходно е понатамошно зголемување на вакцинацијата преку систематска едукација на родителите, адолесцентите и здравствените работници. Второ, потребно е целосно преминување кон организиран HPV-базиран скрининг, кој има поголема чувствителност од традиционалната цитологија и овозможува порано откривање на преканцерозните промени. Трето, неопходно е континуирано јакнење на Националниот регистар за малигни неоплазми и подобрување на квалитетот и комплетноста на епидемиолошките податоци. Дополнително, современите програми за контрола на карциномот на грлото на матката сè повеќе се потпираат на дигитални регистри за имунизација, автоматизирани системи за повикување на скрининг и интегрирани информациски системи. Ваквиот пристап овозможува навремено следење на вакцинацијата, подобра идентификација на ризичните групи и попрецизно планирање на превентивните активности. Главна предност на ова истражување е користењето на официјални национални и меѓународни извори на податоци, што овозможува висока веродостојност на анализата. Дополнително, трудот обезбедува интегриран преглед на состојбата во Северна Македонија во контекст на земјите од Балканот, Европската Унија и глобалните препораки на WHO. Со тоа се добива поширока перспектива за позицијата на земјата и за можностите за понатамошно унапредување на националната програма. Истражувањето има неколку ограничувања. Анализата се заснова на агрегирани официјални податоци, поради што не беше можно да се изврши индивидуално поврзување помеѓу вакцинацијата статус, резултатите од скринингот и појавата на карцином. Исто така, за дел од анализираниот период не се достапни континуирани годишни национални податоци за сите индикатори, што ја ограничува примената на напредни статистички модели за анализа на временските трендови. Дополнително, разликите во методологијата на националните регистри и меѓународните бази на податоци може да доведат до мали варијации во проценетите стапки на инциденца и морталитет. И покрај овие ограничувања, користењето на повеќе официјални извори овозможува конзистентна и релевантна проценка на состојбата. Во иднина е потребно воспоставување на интегрирани аналитички системи кои ќе овозможат поврзување на регистрите за имунизација, скрининг и малигни неоплазми. Таквиот пристап ќе овозможи подетална проценка на долгорочната ефективност на HPV вакцинацијата, идентификација на факторите што влијаат врз вакцинацијата и подобра евалуација на националните програми. Особено значајни ќе бидат студиите што ќе ги следат вакцинираните генерации во наредните две до три децении, кога се очекува целосно да се манифестира заштитниот ефект на вакцинацијата врз инциденцата на инвазивниот карцином.

ЗАКЛУЧОК

Резултатите од оваа студија потврдуваат дека воведувањето на HPV вакцината во редовниот

календар за имунизација претставува една од најзначајните јавно-здравствени интервенции во превенцијата на карциномот на грлото на матката. Анализата на достапните епидемиолошки податоци за Република Северна Македонија, споредени со податоците од земјите на Балканот, Европа и светот, укажува дека земјите кои навремено воспоставиле организирани програми со висок вакцинален опфат бележат значително намалување на инфекциите со високоризичните HPV типови, преканцерозните лезии од висок степен (CIN2+) и инциденцата на инвазивниот карцином на грлото на матката. Во Република Северна Македонија е забележан позитивен тренд на постепено подобрување на опфатот со вакцинација во последните години, но истиот сè уште не е доволен за постигнување на целите дефинирани во глобалната стратегија на Светската здравствена организација за елиминација на карциномот на грлото на матката како јавно-здравствен проблем. Постојат значајни регионални разлики во вакциналниот опфат, како и простор за подобрување на организираниот скрининг и следењето на вакцинираните кохорти. Епидемиолошките анализи покажуваат дека ефектите од вакцинацијата се најизразени кај генерациите вакцинирани пред започнување на сексуалната активност, при што се забележува драматично намалување на циркулацијата на HPV 16 и HPV 18, како и појава на колективен (herd) имунитет во популацијата. Овие резултати се конзистентни со искуствата од повеќе европски држави и претставуваат силна научна потврда за долгорочната ефикасност на националните програми за HPV вакцинација. Студијата укажува дека успехот во контролата на карциномот на грлото на матката не зависи исклучиво од вакцинацијата, туку од интегриран пристап кој ги обединува примарната превенција преку имунизација, секундарната превенција преку организиран HPV-базиран скрининг и навременото лекување на преканцерозните лезии. Само синхронизираното функционирање на овие три столба овозможува значително намалување на морбидитетот и морталитетот. Од аспект на јавното здравје, неопходно е понатамошно зголемување на вакцинацискиот опфат кај девојчињата, континуирано унапредување на програмите за здравствена едукација, активно намалување на вакциналната неодлучност, како и проширување на организираниот скрининг со современи HPV тестови согласно европските препораки. Конечно, резултатите од ова истражување потврдуваат дека Република Северна Македонија располага со реални можности во следната деценија значително да го намали товарот од карциномот на грлото на матката, доколку се обезбеди висок вакцинален опфат, континуирано следење на индикаторите и целосна имплементација на стратегијата 90–70–90 на Светската здравствена организација.

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Profesional paper

KARAKTERISTIKAT EPIDEMIOLOGJIKE TË PACIENTËVE ME KONJUKTIVIT: STUDIM RETROSPEKTIV

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ABSTRAKT

Konjuktiviti është patologjia okulare më e shpesht dhe përbën një shkak të rëndësishëm të paraqitjes së pacientëve në ambulantat oftalmologjike. Simptomat kryesore të konjuktivitit janë: skuqje e syrit, kruarje, djegie, dhimbje, rjedhje e sekretit dhe në raste të rënda mjegullim i pamjes.

Analiza epidemiologjike e rasteve ndihmon në identifikimin e shpërndarjes së sëmundjes dhe karakteristikave demografike të pacientëve që më tutje do të ndihmoj në diagnostikimin dhe trajtimin adekuat të konjuktivitit.

Ne realizuam një studim retrospektiv i bazuar në analizën e të dhënave të pacientëve të diagnostikuar me konjuktivit në periudhën kohore Janar-Qershor të vitit 2026 në repartin e sëmundjeve të syrit në Spitalin klinik në Tetovë.

Nga rezultatet që fituam të cilat përputhen kryesisht edhe me studime të realizuara në qendra të ndryshme në bote mund të konkludojmë se shkaktarë më të shpeshtë të paraqitjes së konjuktiviteve janë ato infektiv si p.sh viruset dhe bakteret. Konkretisht nga 450 raste të analizuara tek mbi 40% shkaktari ishte infektiv dhe paraqitje më të lartë kishte tek gjinia femërore mbi 60% kundër gjinisë mashkullore.

Fjalë kyçe: konjuktiviti, viruse, baktere.

HYRJE

Konjuktiviti është inflamacioni i konjuktivës, membranës së hollë transparente që mbulon sipërfaqen e përparme të sklerës dhe pjesën e brendshme të qepallave. Ai përfaqëson një nga patologjitë okulare më të shpeshta në praktikën klinike dhe është një nga arsyet kryesore të paraqitjes së pacientëve në shërbimet e oftalmologjisë dhe të kujdesit parësor shëndetësor. Megjithëse në shumicën e rasteve ka ecuri beninje dhe vetëkufizuese, konjuktiviti mund të ndikojë ndjeshëm në cilësinë e jetës së pacientëve, të shkaktojë mungesa në shkollë ose në vendin e punës dhe, në raste të veçanta, të çojë në komplikacione okulare nëse nuk diagnostikohet dhe trajtohet në mënyrë të duhur.

Bazuar në etiologjinë, konjuktiviti klasifikohet në forma infektive dhe jo-infektive. Format infektive shkaktohen kryesisht nga viruset dhe bakteret, ndërsa format jo-infektive lidhen me reaksionet alergjike, irrituesit kimikë, traumat ose faktorë të ndryshëm mjedisorë. Konjuktiviti viral konsiderohet forma më e shpeshtë tek të rriturit dhe karakterizohet nga transmetueshmëri e lartë, ndërsa konjuktiviti bakterial është më i zakonshëm tek fëmijët. Konjuktiviti alergjik paraqitet shpesh në individët me histori atopike dhe lidhet ngushtë me ekspozimin ndaj alergjenëve sezonalë ose të përhershëm.(1,2)

Studimet epidemiologjike që analizojnë shpërndarjen e konjuktivitit sipas karakteristikave demografike, si

gjinia dhe mosha, janë të rëndësishme për të kuptuar më mirë modelet e paraqitjes së kësaj patologjie dhe për të mbështetur vendimmarrjen në praktikën klinike. Të dhënat e mbledhura nga institucionet shëndetësore mund të shërbejnë si bazë për përmirësimin e kujdesit ndaj pacientëve dhe për zhvillimin e programeve parandaluese.

Qëllimi i këtij punimi është të paraqesë një analizë epidemiologjike të rasteve me konjuktivit të regjistruara në institucionin shëndetësor gjatë periudhës së studimit, duke analizuar numrin e përgjithshëm të pacientëve dhe shpërndarjen e tyre sipas gjinisë. Rezultatet e këtij studimi synojnë të kontribuojnë në njohjen e karakteristikave epidemiologjike të konjuktivitit në popullatën e studiuar dhe të ofrojnë informacion të dobishëm për praktikën klinike dhe studimet e ardhshme në fushën e oftalmologjisë.(3,4)

MATERIALI DHE METODA

Në studimin tonë kemi përfshirë 450 pacient prej moshës 1-70 vjeç. Studimi bazohet në të dhënat e pacientëve në repartit të syve pranë Spitalit Klinikë të Tetovës, në librin e shënimeve të kontrolleve të pacientëve dhe dokumenta tjera ekzistuese në këtë repart gjatë viti kalendarik Janar – Qershor 2026, gjithashtu janë përdorur dhe materiale nga mjekësia e bazuar në fakte dhe databaza të ndryshme për hulumtime shkencore si Pubmed, Google scholar dhe National library of medicne.

REZULTATET

Në periudhën nga janarë deri në qershor 2026 në shërbimin ambalantor të reparitit të syve pranë Spitalit Klinik tëTetovës janë regjistruar 450 raste me konjuktivit.

Konjuktivitet sipas llojit

Nga numri i përgjithshëm i konjuktiviteve

200 – i kanë takuar konjuktiviteve akute

70 – i kanë takuar konjuktiviteve kronike

80 – i kanë takuar konjuktiviteve alegjike

65 – i kanë takuar konjuktiviteve traumatike

15 - i kanë takuar blefaro-konjuktiviteve

20 - i kanë takuar konjkuktiviteve elektrike.

Konjuktivitet sipas gjinisë

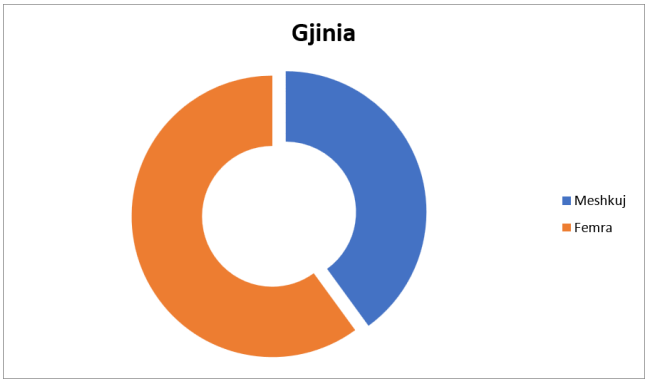
Nga numri i përgjithshëm i konjuktiviteve :

270 i kanë takuar gjinisë femrore

180 i kanë takuar gjinisë mashkullore (tabela .1.)

Gjinia Mashkullore	Gjinia Femrore
180 (40%)	270 (60%)
Gjithësej	450 (100%)

Tabela nr.1 Konjuktivitet sipas gjinisë



Diagrami 1. Struktura sipas gjinisë

Konjktivitet sipas grupmoshës dhe gjinisë

Në grupmoshën 0-15 vjet ka pasur gjithësej 107 konjuktivite nga të cilat 43 kanë qenë meshkuj dhe 64 kanë qenë femra.

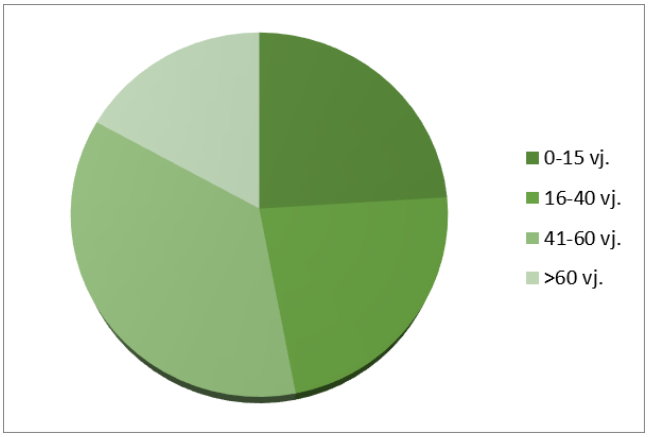
Në grupmoshën 16-40 vjet ka pasur gjithësej 103 konjuktivite nga të cilat 41 kanë qenë meshkuj dhe 62 kanë qenë femra.

Në grupmoshën 41-60 vjet ka pasur gjithësej 158 konjuktivite nga të cilat 63 kanë qenë meshkujt dhe 95 kanë qenë femra.

Në grupmoshën > 60 vjet ka pasur gjithësej 82 konjuktivite nga të cilat 33 kanë qenë meshkuj dhe 49 kanë qenë femra . (tabela.2.)

Mosha	Gjinia Meshkuj	Gjinia Femra	Gjithësej	Përqindja
0-15vj.	43	64	107	24%
16-40vj.	41	62	103	23%
41-60vj.	63	95	158	35%
>61vj.	33	49	82	18%
Gjithësej	180	270	450	100%

Tabela nr.2 Konjuktivitet sipas grupmoshave dhe gjinisë



Digrami 2.Struktura e pacientëve sipas grupmoshës

DISKUTIMI

Konjkuktivitet përbëjnë bindshëm patologjinë më të shpeshtë të sëmundjeve të syrit. Kjo vjen nga vetë fakti se konjuktiva si mbështjellës i jashtëm i syrit është e ekspozuar nën ndikimin e faktorëve të jashtëm qofshin ato biologjik, fizik dhe kimik. Konjktiva si mbështjellës i jashtëm i syrit ka mekanizmat e saja natyrore mbrojtës filmi i lotit që gjihtmonë bën lagien dhe pastrimin e konjuktivave, lizozima që është një ndër substancat më efikase me veprim antimikrobial etj.(6,7,8).

Rezultatet e këtij studimi janë në përputhje me gjetjet e Ramirez et al., të cilët, në një analizë të të dhënave nga urgjencat e Shteteve të Bashkuara, evidentuan një shpërndarje bimodale të rasteve të konjuktivitit sipas moshës, me frekuencën më të lartë te fëmijët dhe një rritje të dytë në moshën e hershme të rritur. Gjithashtu, autorët raportuan një frekuencë më të lartë te femrat e rritura dhe një model të dallueshëm sezonal të sëmundjes.

Në mënyrë të ngjashme, një studim multicentrik i kryer në SHBA dhe Izrael tregoi se konjuktiviti akut infektiv ishte më shpesh i lidhur me patogjenë viralë sesa me ata bakterialë. Në këtë studim, 60% e pacientëve ishin femra dhe në 60% të rasteve ishin të përfshirë të dy sytë. Këto të dhëna mbështesin rëndësinë e analizimit të karakteristikave demografike dhe klinike të pacientëve me konjuktivit në vlerësimin e profilit epidemiologjik të sëmundjes.(11,12).

Për të bërë diagnostifikimin e drejtë etiologjik të konjuktiviteve oftalmologët udhëheqin në bazë të pasqyrës klinike dhe simptomave.

Në shumicën e rasteve duhet bërë edhe egzaminime plotësusese si strisho për analizë mikrobiologjike dhe antibiogram, teste alergogjike, imunoflurosecence etj.

PËRFUNDIMI

Në bazë të rezultateve të fituara kemi ardhur në përfundim se: lloji më i shpeshtë i konjuktiviteve janë konjuktivitet akute me 200 raste ose 44.4%, gjinia më e prekur nga konjuktivitet është gjinia femrore me 270 raste ose 60%, grupmosha më e prekur nga keratokonjuktivitet është ajo 41-60 vjet me 158 raste ose 35%.

Diagnostikimi dhe trajtimi i saktë i konjuktiviteve ndikon drejtpërsëdrejti në kualitetin e jetës së pacientëve prandaj detektimi i shkaktarëve dhe analizat epidemiologjike të kësaj sëmundje janë shum të rëndësishme në praktikën klinike oftalmologjike. Format e këtyre studimeve janë më se të domosdoshme në praktikat klinike.

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Profesional paper

THYROID STATUS OF PREMATURE NEWBORNS IN THE REPUBLIC OF NORTH MACEDONIA

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ABSTRACT

Thyroid hormones are extremely important for the growth and development of the nervous system during the newborn period and childhood. A number of studies point to the fact that, unlike term infants, preterm infants are more likely to have thyroid status abnormalities due to their immaturity, immature hypothalamic-pituitary-thyroid axis, and associated comorbidities. One of the common occurrences in preterm infants is transient hypothyroidism which is defined as a condition of low serum thyroid hormone levels with normal / slightly decreased TSH values. This phenomenon is directly proportional to the degree of immaturity of the newborn, and gestational week.

In North Macedonia, despite the numerous published analyses of thyroid screening, no specific analysis has been made of the findings in preterm infants. Taking into account the debate and controversy discussed on this issue in scientific circles, the aim of this paper is to analyse the thyroid status of preterm infants.

Keywords : transient hypothyroidism, preterm infants, screening program

INTRODUCTION

According to the World Health Organization, premature babies are all babies born before the 37 weeks of gestation. These newborns are classified into three categories depending on the gestational week, namely: extremely premature (less than 28 weeks), very premature (28 to 32 weeks), and moderately to late premature (32 to 37 weeks). According to the same institution, approximately 15,000,000 premature babies are born each year, of which over one million die from complications related to prematurity itself. Accordingly, prematurity ranks as the most common cause of mortality in children under five years of age, although at least ¾ of them can be avoided as a result of advanced neonatal care.

Preterm infants have a relatively immature hypothalamic-pituitary-thyroid axis, as well as a high prevalence of neonatal comorbidities, including respiratory distress, hypoxia, malnutrition, gastrointestinal and cardiac dysfunction, sepsis, and cerebral pathology. As a result, they are more likely to develop transient primary hypothyroidism and transient hypothyroxinemia syndrome of prematurity, which is likely to represent transient hypothalamic-pituitary hypothyroidism and/or nonthyroidal illness (NTI , low T3 syndrome). [1]

Thyroid function in premature infants reflects the relative immaturity of the hypothalamic-pituitary-thyroid axis compared with term infants. Cord blood samples taken from the umbilical cord (cordocentesis) show a progressive increase in the concentration of TSH, TBG, T4 and T3 in fetuses, directly proportional to their degree of maturity. Immediately after birth, term infants show a marked increase in TSH and T4 , but this

increase is less pronounced in preterm infants, in whom a dramatic decrease in T4 concentration occurs over the next one to two weeks [2] .

In order to detect congenital hypothyroidism in newborns early, mandatory screening is carried out within the first 48 hours after birth. ESPE (European Society for Pediatric Endocrinology) also in 2014 it was recommended to be implemented worldwide in addition to the first screening after birth, and a second screening after the second week of life for certain categories of newborns, including premature infants. This is recommended because of the possibility of congenital hypothyroidism with delayed TSH elevation, a condition that would not be detected or overlooked at the initial screening in premature infants precisely because of this immature axis and the associated numerous comorbidities such as respiratory distress syndrome, intensive care unit admission, sepsis, drug administration, administration of total parenteral nutrition, and other factors that affect thyroid status.

Given the crucial importance of screening for the detection of congenital hypothyroidism, a large number of studies have been conducted to determine the best strategy for screening premature infants, studies that still result in controversy on this issue in the scientific and professional community. A strategy for quickly and efficiently distinguishing physiological hypothyroxinemia from true hypothyroidism, which requires treatment, has not yet been fully elaborated. However, TSH and T4 screening are the two most commonly used forms of screening worldwide. With this in mind, several strategies are available for conducting screening for congenital hypothyroidism, as follows [3]:

Primary T4 and secondary TSH strategy. According to this strategy, all newborns are screened for total thyroxine concentration, and TSH analysis is also performed for newborns with the lowest thyroxine concentration (T4 <13 μg/dL). This approach allows for the detection of central and peripheral hypothyroidism. However, it should be borne in mind that this combination of high thyroxine concentration but low TSH concentration is normal in premature babies and in sick newborns, as well as in newborns with TBG deficiency, or deficiency of other binding proteins.

Primary TSH with or without T4. The main advantage of this strategy is the increased detection of partially compensated hypothyroidism.

Duality of T4 and TSH . This strategy allows for increased detection of central hypothyroidism.

Free T4 strategy. Although quite sensitive, this strategy is not in common use.

Although dozens of arguments can be made for the benefits of TSH or T4 as primary markers for congenital hypothyroidism, both are accompanied by a number of weaknesses. The following are the major disadvantages of the TSH approach: failure to detect secondary and tertiary hypothyroidism; failure to detect thyroxine binding globulin (TBG) deficiency ; failure to detect delayed growth in TSH levels ; increased false-positive values in infants less than three days old. The main disadvantages of using T4 as a primary marker for the detection of congenital hypothyroidism are: failure to detect infants with elevated TSH but normal T4 concentrations; and increased need for repeat analyses due to low T4 levels with normal TSH concentrations [4].

A mandatory screening program for congenital hypothyroidism is implemented in the Republic of North Macedonia, using the TSH marker as the primary marker for the detection of congenital hypothyroidism. A study of TSH values in the period 2002-2017 has shown the results presented in the following table (Table 1).

Table 1. Number of screened newborns and percentage of newborns with tsh>5 miu/l in the period 2002 – 2017 [5]

Period	Number of screened newborns	TSH (± SD)	TSH > 5 mIU/L (%)
4.2002	7225	6.73 ± 1.72	4.26
2003	9855	6.32+±1.31	5.88
2004	10225	5.82 ± 0.8	2.74
2005	9678	5.77 ± 0.76	1.34
2006	9152	5.92 ± 0.91	1.75
2007	21770	5.86 ± 1.48	2.48
2008	21973	6.49 ± 1.48	3.18
2009	22826	6.31 ± 1.2	2.95
2010	23558	6.38 ± 1.33	2.88
2011	21967	6.3 ± 1.26	3.29
2012	23101	6.29 ± 1.14	3.31
2013	22807	6.16 ± 1.11	2.85
2014	23518	6.72 ± 1.71	3.12
2015	22742	6.88 ± 1.51	3.6
2016	22591	7.23 ± 1.72	3.8
2017	21604	6.76 ± 1.11	4.06
Total	294592	6.37 ± 1.25	3.22

A literature review indicates hundreds of analyses of

thyroid status in premature infants in different parts of the world. Despite the large number of studies conducted worldwide, there is still no consensus on the best way to detect hypothyroidism in premature infants, including several aspects such as the most appropriate time for sampling, the method of interpreting the results, cut-off values in this category of children, views on the need to administer therapy in terms of its benefits, etc.

Zung and co-authors indicate that additional risk factors that affect thyroid status (delayed elevation of TSH) include associated comorbidities (DAP, pneumothorax), mechanical ventilation, transfusion, and antibiotic therapy [6] Cavarzere and coauthors suggest that a second screening should be performed in newborns under 2500 g, as it allows detection of congenital hypothyroidism that would otherwise be overlooked at the first screening [7].

An analysis of 24 premature infants detected by TSH screening with cut-off values >=10 mlU/L , out of a total of 299,204 screened infants in Lombardy (Italy), demonstrates a high incidence of transient hypothyroidism, and that it is extremely important to conduct a re-evaluation for a definitive diagnosis. Namely, in the specific study only 21% of cases were detected by the first screening, while as many as 73.9% were detected by the second screening and about 5% by the third screening [8].

METHODS AND MATERIALS

To determine the thyroid status of premature infants in the Republic of North Macedonia, an analysis of approximately 16,000 newborns was conducted. Data on newborns and TSH screening results were taken from the screening program for congenital hypothyroidism regularly performed at the Clinic for Children's Diseases in Skopje. The data were processed with eview. The analysis enabled the identification of 946 premature infants, i.e. approximately 5.9% of the total newborns in the given period fall into the category of premature babies. A first screening was conducted for all of them. However, according to the results of the regular first screening, the need for a second and third screening was observed in only 0.4% of premature babies.

RESULTS

The conducted research shows an almost equal gender structure of premature babies. Namely, about 46% of them are male and the rest female. However, it is worth noting that due to omissions in filling in the data, the gender of around 8% could not be determined, as can be noted from chart.1

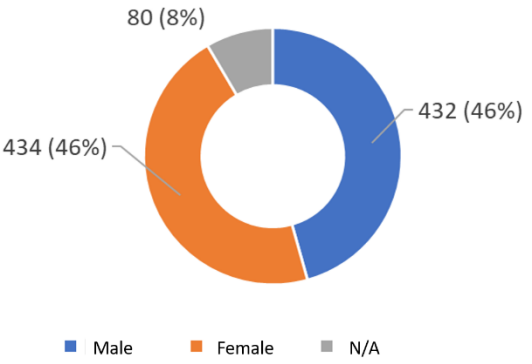

Chart 1. Gender structure of premature infants

Quite expectedly, the largest number of premature newborns were born at the University Clinic of Gynecology and Obstetrics, with almost half of the total number of premature newborns born in the entire territory of the Republic of North Macedonia being born within this institution (Table 2).

Table 2. Premature infants by place of birth

Institution	n	%
Public Health Institution University Clinic for Gynecology and Obstetrics	453	47.73
Acibadem Sistina Primary Health Center	107	11.28
Public Health Institution Mother Teresa	69	7.27
Public Health Unit Clinical Hospital Tetovo	40	4.21
Public Health Unit General Hospital with Extended Activities - Prilep	36	3.79
Private Health Institution. ReMedica	35	3.69
Public Health Unit Clinical Hospital Bitola	33	3.48
Primary Health Care Special Hospital "Fertility"	26	2.74
Public Health Institution Strumica General Hospital	23	2.42
Public Health Institution General Hospital "Dr. Ferid Murad"-Gostivar	15	1.58
Public Health Institution Struga General Hospital	15	1.58
Public Health Institution Kumanovo General Hospital	15	1.58
Public Health Institution Ohrid General Hospital	14	1.48
Public Health Unit Clinical Hospital Shtip	9	0.95
Other	59	6.22

In terms of birth weight, almost 2/3 of preterm infants belonged to the category of up to 2499 grams, with the majority of them having a birth weight between 1500-2499 grams (Chart 2.)

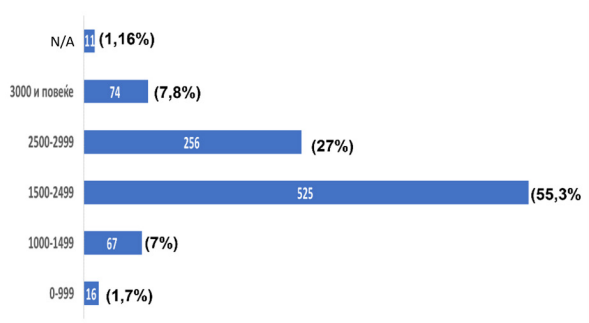

Chart 2. Premature infants by birth weight

Viewed by gestational week, the number of extremely premature infants in the structure of preterm infants is small. Namely, as can be seen from the data presented in chart 3, about 2/3 of the total number of preterm infants were born between 34 and 36 gestational weeks, and only 18, or 1.9%, were born between 24 and 27 gestational weeks.

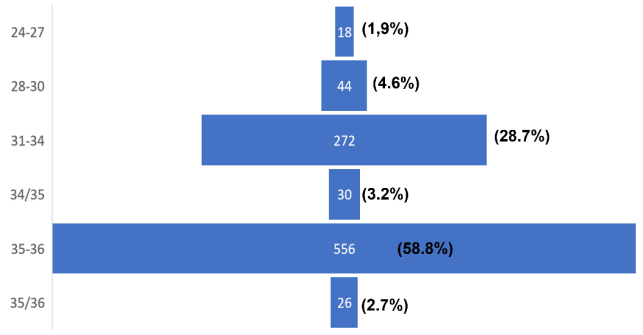

Chart 3. Premature infants by gestational week

The results of regular screening showed a very small number of cases with elevated TSH , according to established standards. As can be seen from the data presented in Chart no. 4, in 4/5 of the total number of premature newborns the TSH concentration was between 0.01 and 2.99 mlU/L . Only four newborns, or 0.4% of their total number, showed an elevation of the TSH concentration , or above 10 mlU/L .

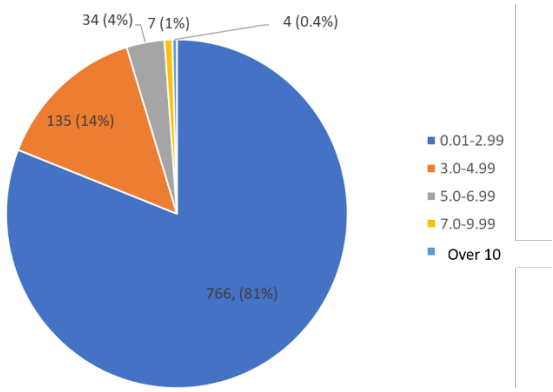

Chart 4. Results of the first screening

According to the results of the first screening, the need for a second screening was noted in four patients. In three of them, the first drop was taken on time according to the protocol, while in one patient it was taken prematurely, i.e. only 45 minutes after birth. Therefore, the initial value in this patient is higher, i.e. 28.9 mlU/L . In all four patients, a second and third drop were taken, but the results were within the acceptable reference values, tab.3.

Table 3. Second and third screening in premature infants

Data at birth First Second					Screening results Third				
Date	M/F	Time	Birth weight	Gest. week	Date	Time	Result	Result	Result
10.01.2020	F	10:40	1730	32	19.01.2020	11:00	10.60	0.40	0.35
20.01.2020	F	09:34	2530	36	21.01.2020	09:20	10.09	7.76	7.78
10.03.2020	M	13:55	2430	36	10.03.2020	14:40	28.90	5.50	5.40
15.04.2020	F	08:50	2030	36	18.04.2020	05:00	11.20	8.81	8.49

The results of the study show that the concentration of TSH varies depending on the gestational week. For example: in newborns born at 24 weeks of gestation, the average concentration of TSH is 0.7 mlU/L , in newborns born at 25 weeks of gestation, the average concentration of TSH is 0.522 mlU/L , in newborns born at 26 weeks of gestation, the average concentration of TSH is 1.194 mlU/L , in newborns born at 27 weeks of gestation, the average concentration of TSH is 0.845 mlU/L , etc. In addition, the minimum and maximum values of TSH concentration differ depending on the gestational week, which can be clearly seen from the data presented in the following table (Table 4).

Table 4.TSH variations depending on gestational age

G.week	Average	Max	Min	SD	Probability	Observations
24	0.70	0.93	0.5	0.19	0.80	4
25	0.52	1.58	0.06	0.61	0.53	5
26	1,19	2.30	0.23	0.96	0.73	5
27	0.84	1.29	0.44	0.36	0.87	4
28	0.96	4.49	0.03	1.37	0.02	11
29	1.01	3.79	0.05	1.08	0.02	14
30	1.68	8.27	0.13	1.98	0	19
31	1.78	5.50	0.04	1.41	0.04	32
32	1.98	10.60	0.01	1.98	0	32
33	1.80	4.45	0.03	3.42	0	87
34	1.91	7.07	0.01	1.64	0	121
35	2.14	9.65	0.01	1.71	0	201
36	2.03	28.9	0.01	2.12	0	354
33/34	1.38	3.49	0.05	1.47	0.75	4
34/35	2.13	6.48	0.02	1.68	0.19	26
35/36	1.69	5.75	0.05	1.45	0.09	22
36/37	2.70	3.44	1.34	1.18	0.76	3

The following table presents summarized data on variations in TSH concentration , depending on the category of prematurity, according to the World Health Organization classification (Table 5).

Table 5.TSH variations depending on the category of prematurity according to WHO

Results	Prematurity category		
	Extremely premature	Very premature	Moderate to late prematurity
Average	0.82	1.49	1.96
Maximum	2.30	8.27	28.90
Minimum	0.06	0.03	0.01
Standard dev.	0.64	1.53	1.81
Observations	18	76	851

As can be seen, according to the research, extremely premature infants are characterized by a lower TSH concentration compared to the other two categories. In this category of infants, the average TSH concentration is 0.82 mlU/L with the minimum and maximum values varying from 0.06 mlU/L to 2.3 mlU/L . In the category of very premature infants, the average TSH concentration is 1.5 mlU/L with the minimum and maximum values varying from 0.03 mlU/L to 8.2 mlU/L . In the category of late premature infants, the average TSH concentration is almost 2 mlU/L with the minimum and maximum values varying from 0.01 mlU/L to 28.9 mlU/L .

DISCUSSION

The research conducted clearly indicates that the first screening, if carried out according to established protocols, detects a small number of cases of premature infants with congenital hypothyroidism. In this particular case, only 0.4% of premature infants were detected through the first screening.

There is a possibility that premature infants with primary hypothyroidism and delayed TSH elevation may not have been detected at the first screening. Namely, results indicating low TSH levels may have been false negatives. These omissions should be detected at the repeat test. In addition, in infants with transient hypothyroxinemia and transient physiologic TSH elevation, the second screening may often indicate normal thyroid function instead of the initial false positive result [9].

Accordingly, it is possible that all four cases in which the first screening indicated the need for a second screening were false positives, given that in all of these cases the second screening showed results that were within acceptable reference values. On the other hand, given that it is not a mandatory practice to conduct a second screening, it is possible that the remaining 99.6% of preterm infants had a series of false negative results.

In the case of the conducted research, this possibility is also confirmed by the results of the statistical processing of the data. First of all, the statistical analysis of the data shows lower levels of TSH concentration in extremely premature newborns, although from a theoretical point of view the trend should be the opposite. Second, the statistical processing of the data clearly confirms that in late premature newborns it is very unlikely that an increased TSH concentration will manifest itself. However, in our case, out of the four identified cases with an increased TSH concentration according to the first screening, as many as three were born at 36 weeks of gestation.

Hence, it is quite logical that the request of the relevant international organizations, and a series of studies worldwide, clearly indicate that the first screening is not sufficient, due to the possibility of delayed evaluation of TSH concentration , especially in premature newborns. For example, Hemmati [10] and co-authors, through an analysis of 320,886 newborns, of which 15,381 were detected preterm, have come to the conclusion that re-screening should be performed in premature newborns because, according to their results, about 31.3% (out of

a total of 355 premature newborns with increased TSH levels) of patients with increased TSH were detected during the first screening, and an additional 43.9% during the second screening (performed two weeks later).

So the second screening is suggested for congenital hypothyroidism with delayed TSH elevation , a condition that would be overlooked in the initial screening in premature babies precisely because of that immature axis and the numerous associated comorbidities.

In order to increase the efficiency of the entire screening process, it is worth emphasizing the medical and economic significance of timely blood sampling. In the specific case, as was pointed out in one of the four re-screened patients, a drop of blood was taken too early in the first screening, but, from a purely mathematical point of view, this is 25% of the total number of detected cases. In addition, it was observed in the category of premature newborns who did not have an increased concentration of TSH dozens of cases of not taking the first sample on time. This means that in several cases the reliability of the results themselves might have been compromised, and at the same time unnecessary expenses have incurred because the first screening itself did not result in reliable results.

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Review

TINNITUS: A COMPREHENSIVE REVIEW OF CURRENT EVIDENCE

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ABSTRACT

Tinnitus is the perception of sound without external acoustic stimulus. It is a common auditory symptom that can substantially affect quality of life. Although frequently associated with hearing loss, its underlying mechanisms are complex and remain incompletely understood. This review summarizes current evidence on the epidemiology, clinical characteristics, pathophysiology, risk factors, assessment, and management of tinnitus, with emphasis on recent developments. Current evidence suggests that tinnitus results from complex interactions between peripheral auditory abnormalities, central neural plasticity, abnormal neural activity, and non-auditory networks involved in attention, cognition, emotion, and autonomic regulation. Biological, audiological, psychological, lifestyle, and environmental factors may further modulate the perception and impact of tinnitus. Comprehensive assessment should include otological and audiological evaluation, psychoacoustic testing, and validated patient-reported outcome measures. Management should be individualized and may include pharmacotherapy, auditory rehabilitation, sound-based interventions, tinnitus retraining therapy, cognitive behavioral therapy, and selected neuromodulatory approaches. Despite substantial advances in understanding tinnitus, no universally effective treatment is currently available. A multidimensional and individualized approach to assessment and management is therefore essential.

Keywords: tinnitus, pathophysiology, tinnitus assessment; tinnitus treatment

INTRODUCTION

Tinnitus is the perception of sound without external acoustic stimulus [1]. The term "tinnitus" is derived from the Latin word tinnire, meaning "to ring" [2]. Many people may experience transient ear noises, also called brief spontaneous tinnitus, which are often described as a whistling sound, accompanied by the perception of hearing loss. The event is unilateral and generally resolve within a few minutes [3]. It is necessary to distinguish these noises from pathological tinnitus. Pathologic tinnitus is defined as head noise that lasts at least five minutes and occurs more than once a week. In the International Classification of Diseases,11th revision (ICD-11), tinnitus is described as "A nonspecific symptom of hearing disorder characterized by the sensation of buzzing, ringing, clicking, pulsations, and other noises in the ear in the absence of appropriate corresponding external stimuli and in the absence of what the examiner can hear with a stethoscope" [4].

There is a recent international multidisciplinary proposal that the tinnitus without and with associated suffering should be differentiated by distinct terms. The following definitions are proposed: "Tinnitus is the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source, which becomes Tinnitus disorder "when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioral changes and functional disability" [5].

Tinnitus is one of the most common otological symptoms encountered in clinical practice and represents a

significant public health challenge. Chronic tinnitus can substantially impair quality of life, affecting sleep, concentration, emotional well-being, and work productivity. Despite decades of research, its underlying mechanisms remain incompletely understood, and no universally effective cure is currently available. The aim of this review is to summarize current knowledge on the epidemiology, pathophysiology, diagnosis, and management of tinnitus, with particular emphasis on recent advances in therapeutic approaches.

PREVALENCE OF TINNITUS

The meta-analysis of the global prevalence and incidence of tinnitus, including published articles in the period 1972-2021, showed pooled prevalence of tinnitus among adults 14.4% (ranging from 4.1% to 37.2%), 14.1% in men and 13.1% in women. The increased prevalence was associated with the age: 9.7% in adults aged 18-44 years, 13.7% among those aged 45-64 years, and 23.6% among those aged ≥ 65 years. The pooled prevalence of severe tinnitus was 2.3% (ranging from 0.5% to 12.6%), and the pooled prevalence of chronic tinnitus was 9.8% [6].

In the United States, the overall prevalence of tinnitus in 2014 was 11.2% among people aged 18 to 85 years which is higher than 9.6% prevalence of tinnitus estimated in 2007 [7]. Shargorodsky et al. (2010) reported a higher prevalence of tinnitus 25.3%, 26.1% in men and 24.6% in women. The prevalence of frequent tinnitus increases with age, reaches a peak in the age group 60-69 years, and then decreases. At age < 30 years it was 2.6%; 30-39 years 4.1%; 40-49 years 6.6%; 50-59 years 12.5%; 60-69 years 14.3%; 70-79 years 13.8% and at age ≥ 80 years 12.5% [8].

In Europe, the prevalence of tinnitus in adults was 14.7% (ranging from 8.7% to 28.3%),14% in men and 15.2% in women. A cross-sectional European Tinnitus Survey (ETS) was conducted in 12 European Union countries in the period 2017-2018. Tinnitus prevalence significantly increased with increasing age and worsening of hearing status. The prevalence of any tinnitus in different age groups was as follows: 18-34 years 7.2%, 35-44 years 10%, 45-54 years 13.3%, 55-64 years 18.1%, 65-74 years 26.3% and ≥ 75 years 30.4%. The prevalence of bothersome tinnitus was 6%, 5% in men and 6.6% in women, and the prevalence of severe tinnitus was 1.2%, 1% in men and 1.4% in women [9].

Types of tinnitus and characteristics

Tinnitus is commonly classified as objective or subjective according to whether the sound can be heard by others. Objective tinnitus is usually rhythmic or pulsatile and, rarely, can be detected by auscultation. Pulsatile tinnitus may be synchronous with the heartbeat, suggesting a vascular origin, or asynchronous, suggesting middle-ear or palatal myoclonus [2]. Objective tinnitus may also occur with a patulous Eustachian tube [10].

In approximately 99% of all cases tinnitus is subjective and audible only to the patient. Perceived sounds include ringing, buzzing, clicking, hissing, and other noises [11]. Tinnitus may be tonal or noise-like, constant or intermittent, and localized to one or both ears or the head [2]. Bilateral tinnitus is more prevalent than the unilateral and left ear unilateral tinnitus is more common than right ear tinnitus [12]. Unilateral tinnitus, particularly with asymmetric hearing loss, requires careful evaluation because of possible retrocochlear pathology, including vestibular schwannoma, although it may also occur in Ménière's disease and idiopathic acute sensorineural hearing loss [13,14]. Tinnitus is generally classified as acute or chronic. Although the 2014 Clinical Practice Guideline defined persistent tinnitus as lasting ≥ 6 months [3], a more recent international consensus proposed a 3-month cut-off between acute and chronic tinnitus [5]. Tinnitus is usually high-pitched, particularly in noise-induced hearing loss and presbycusis [15,16], whereas Ménière's disease and otosclerosis are more often associated with lower-pitched tinnitus [17,18]. Tinnitus loudness expressed in dB sensation level (SL) is typically lower when the comparison frequencies are inside (2-3 dB) rather than outside (10-15 dB) the tinnitus region [19].

Theories of tinnitus generation

Tinnitus is thought to result from abnormal neural activity at some point or points in the auditory pathway which is erroneously interpreted by the brain as sound [20], although no single theory explains all clinical presentations. The theory related to the edge frequency of the audiogram proposes that reduced spontaneous or low-level stimulus-induced activity in auditory nerve fibres corresponding to hearing loss decreases lateral inhibition in central auditory structures. This may produce hypersensitivity and hyperactivity in neurons near the audiometric edge [21].

Peripheral auditory damage from noise exposure, aging, otological or neurological disease, infection, or ototoxic drugs may reduce auditory input and induce

central changes. According to the theory of homeostatic plasticity, the reduction in auditory input and neuronal inhibition is compensated by increased neuronal excitation in an attempt to maintain a stable mean firing rate. This increased neuronal excitability may amplify spontaneous neural activity or "neural noise", resulting in the perception of tinnitus. Figure 1 illustrates proposed mechanisms of tinnitus generation.

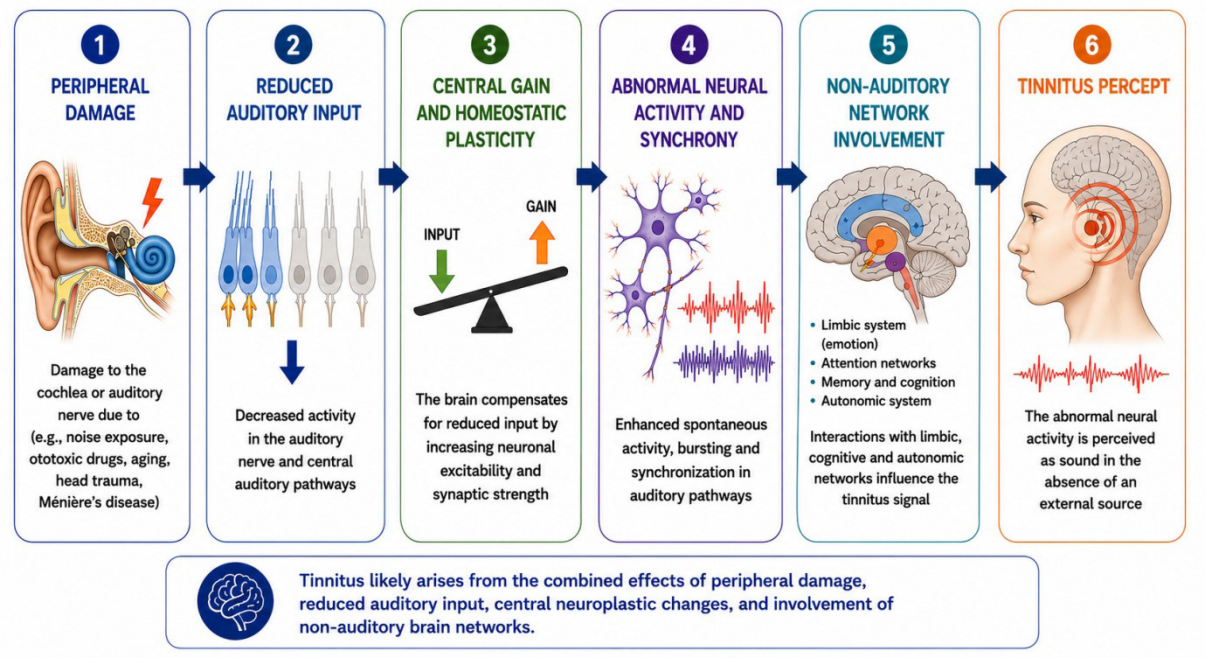

Figure 1. Proposed mechanisms of tinnitus generation

Peripheral damage may also induce changes in tonotopic organization, with increased neural activity in cortical regions corresponding to the transition between normal and impaired hearing [22]. Recent evidence indicates that macroscopic tonotopic reorganization is not essential for tinnitus, particularly in people with normal hearing or mild hearing loss [23]. Neuroimaging further indicates that tinnitus involves non-auditory networks related to attention, memory, and emotion [24]. Functional magnetic resonance imaging (fMRI) scans from patients living with tinnitus showed areas of the brain with abnormal increases in neural activity in the brainstem, thalamus, limbic and hippocampal regions, with decreased activity in frontal and precuneus areas [25].

No single pathophysiological model, including peripheral, central, gating, somatosensory, inflammatory, psychological, and perception-based models, comprehensively explains tinnitus, supporting a multifactorial understanding of its mechanisms [26].

Risk factors for development and experience of tinnitus

The main risk factor for developing tinnitus is hearing loss [27]. Approximately 90% of tinnitus patients had some degree of hearing impairment. Relevant otological factors include noise-induced hearing loss, presbycusis, otosclerosis, ototoxic medications, cerumen impaction, otitis media, Ménière's disease, labyrinthitis, mastoiditis, and vestibular schwannoma [28,29]. Chronic tinnitus is most often associated with NIHL and presbycusis. NIHL is one of the most prevalent occupational diseases in the world [30].

A positive causal association has been found between tinnitus and some non-otological risk factors, i.e., chronic obstructive pulmonary disease, hyperlipidemia, and depression [28]. Tinnitus is increasingly viewed as a condition influenced by systemic and vascular factors [31], somatization, smoking, anxiety, poor speech recognition ability in noise, post-traumatic stress disorder and insomnia [32,33].

Normal hearing thresholds has long been considered an indicator of the absence of cochlear damage. More recent studies have shown that even if hearing is normal at standard audiometric frequencies (125-8000 Hz),

hearing impairment may still be present. Noise exposure and aging may cause "hidden hearing loss" or cochlear synaptopathy, characterized by loss of synapses between inner hair cells and auditory nerve fibres despite preserved hair cells. In tinnitus patients with normal audiograms, reduced auditory brainstem response wave I (generated by primary auditory nerve fibers) with preserved more centrally generated wave V has been reported [34].

In some patients with tinnitus and normal hearing at standard audiometric frequencies, hearing loss is detected at frequencies above 8000 Hz [35,36]. Extended high-frequency (EHF) audiometry including the frequencies from 9000 to 16000 or 20000 Hz may therefore provide additional information.

The perception and impact of tinnitus are shaped by interacting biological, audiological, psychological, lifestyle, and environmental factors. These factors may influence tinnitus intensity, salience, emotional significance, and persistence, contributing to individual differences in distress. Figure 2 illustrates these interactions.

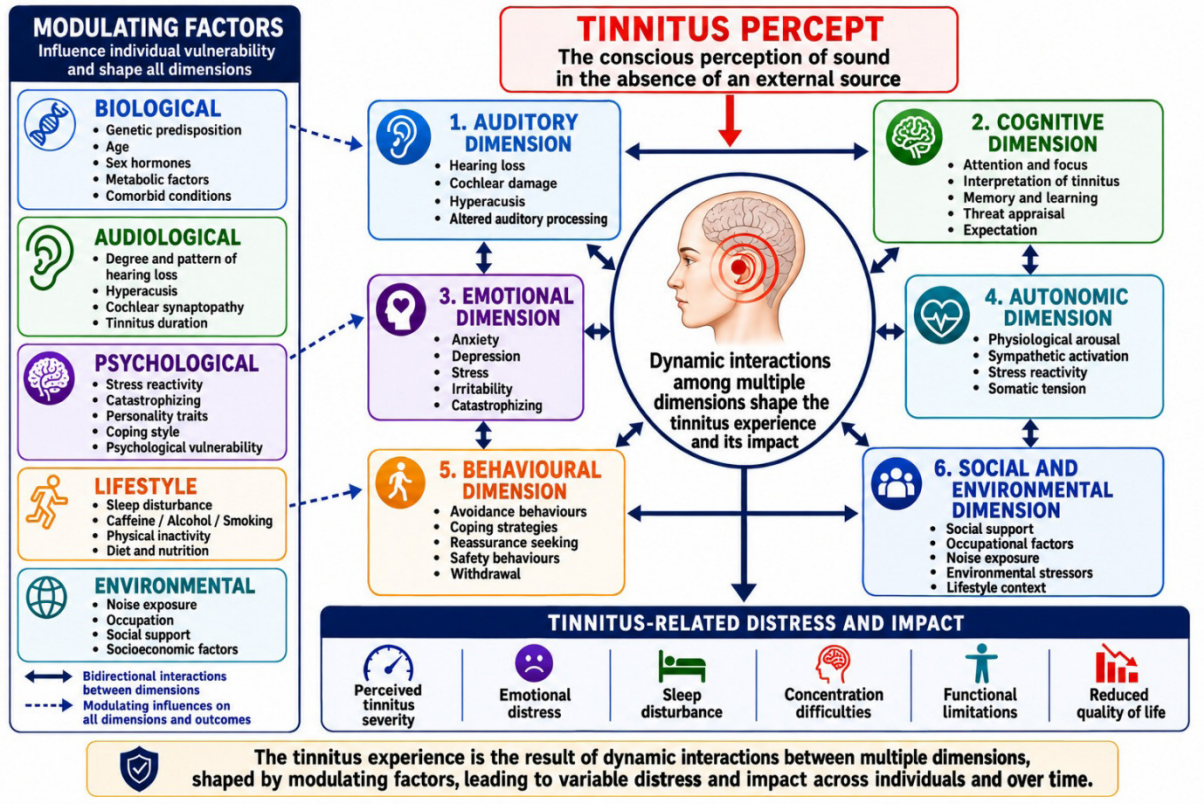

Figure 2. Interaction between different factors for tinnitus perception

Biological factors such as genetic predisposition, age, hormonal and metabolic influences, and comorbidities may affect vulnerability, while audiological factors, including hearing loss, hyperacusis, cochlear synaptopathy, and tinnitus duration, may influence its auditory representation. Psychological, lifestyle, and environmental factors can further affect interpretation, attention, symptom severity, and distress. Their interaction across auditory, cognitive, emotional, autonomic, behavioral, and social dimensions determines the overall impact of tinnitus.

Tinnitus and hyperacusis

Hyperacusis, or decreased sound tolerance, is characterized by discomfort or distress in response to sounds that most people consider tolerable. Unlike misophonia, which involves specific sounds, hyperacusis may affect a broad range of everyday sounds, from distant traffic to household appliances [37]. Individuals may experience irritation, stress, fatigue, pain, or fear, with

consequences for social, occupational, and academic functioning. Approximately 40% of patients with tinnitus report some degree of hyperacusis, while up to 86% of individuals with hyperacusis report tinnitus. However, worsening of tinnitus in response to loud sounds alone should not be classified as hyperacusis [2].

Tinnitus in children

Estimating pediatric tinnitus prevalence is difficult because children may not spontaneously report symptoms and some studies rely on parental observations. In one large study of 7-year-old children, 13.6% had tinnitus, while 33% reported ringing when directly asked; more than 75% had not spontaneously complained to their parents [38].

Auditory deprivation followed by auditory stimulation in children with cochlear implants may involve cross-modal neuroplasticity and reorganization of sensory networks, mechanisms that may also influence tinnitus in children with severe hearing loss [39].

Tinnitus assessment

Comprehensive tinnitus assessment includes otorhinolaryngologic examination, hearing assessment, validated questionnaires, and psychoacoustic testing, including pitch and loudness matching, masking, and residual inhibition (Figure 3). Additional investigations may be indicated in selected cases [40].

Investigations of the psychoacoustic characteristics of tinnitus showed that tinnitus pitch generally falls within the range of hearing impairment, although correspondence with the audiometric edge occurs in only approximately 15% of patients. Majority of patients had tinnitus pitch in the range from 3000 to 8000 Hz, corresponding to the range of hearing loss. Tinnitus is usually masked by ipsilateral noise in most patients, and 70-85% may experience residual inhibition [41,42].

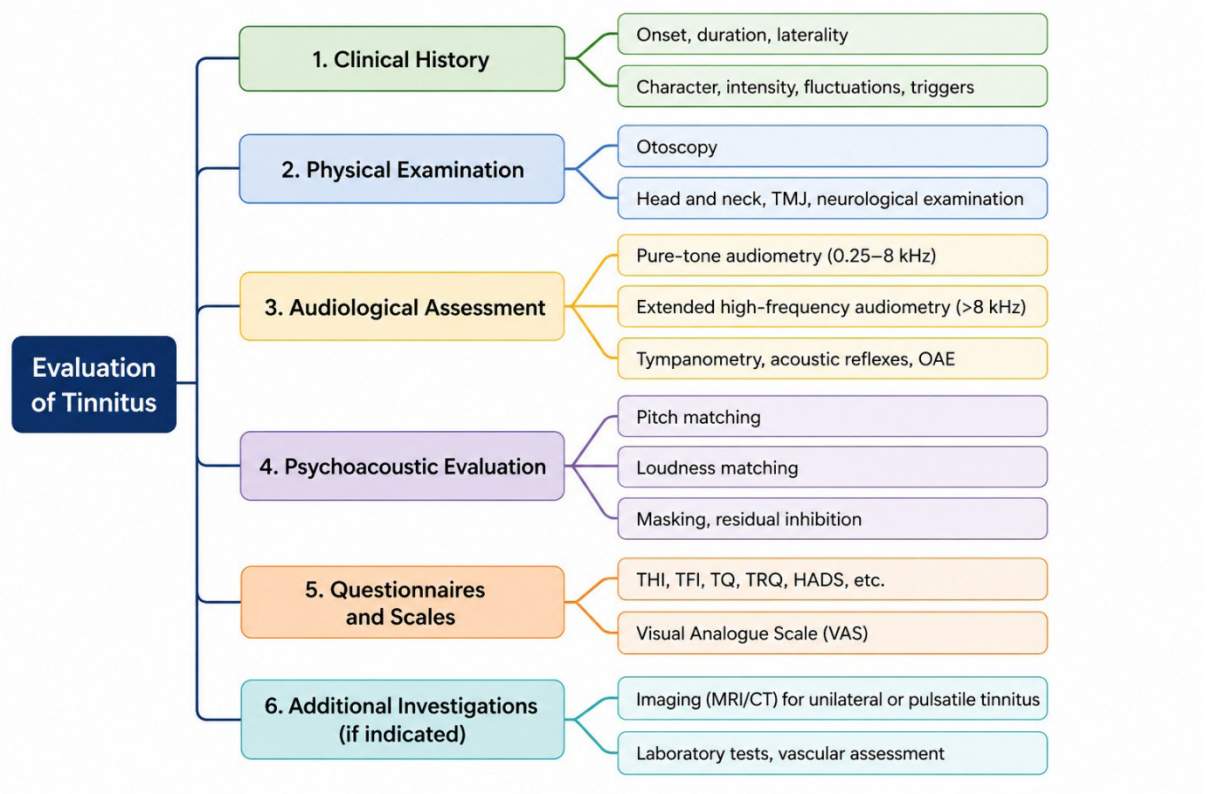

Figure 3. Steps in tinnitus evaluation

Tinnitus Handicap Inventory (THI) and Tinnitus Functional Index (TFI) are widely used questionnaires for subjective assessment of tinnitus severity. The THI contains 25 items covering functional, emotional, and catastrophic domains and uses a three-point response scale: Yes (4 points), Sometimes (2 points), and No (0

points). The original English version demonstrated excellent internal consistency (Cronbach's α = 0.93) [43].

The TFI also contains 25 items and evaluates eight domains, including annoyance, sense of control, cognitive interference, sleep disturbance, auditory difficulties, relaxation, quality of life, and emotional distress. Responses are scored on a 10-point scale, producing a total score from 0 to 100. The internal consistency is excellent (Cronbach's α = 0.97) [44].

A visual analog scale (VAS) may be used to assess tinnitus loudness, annoyance, and overall impact. Most patients rate loudness as moderate, while annoyance may differ according to tinnitus quality. In one study, mean VAS-annoyance was 5.47 for tonal and 6.67 for noise-like tinnitus [45].

Treatment of tinnitus

Tinnitus treatment remains challenging and should be individualized. Figure 4 illustrates tinnitus treatment options. Pharmacological approaches include antidepressants, anticonvulsants, benzodiazepines, glutamatergic agents, muscle relaxants, and medications for vertigo, while herbal and dietary supplements, such as extract of Ginkgo biloba, zinc, magnesium, melatonin, vitamin B3 and vitamin B12 are also commonly used, although their evidence varies [46].

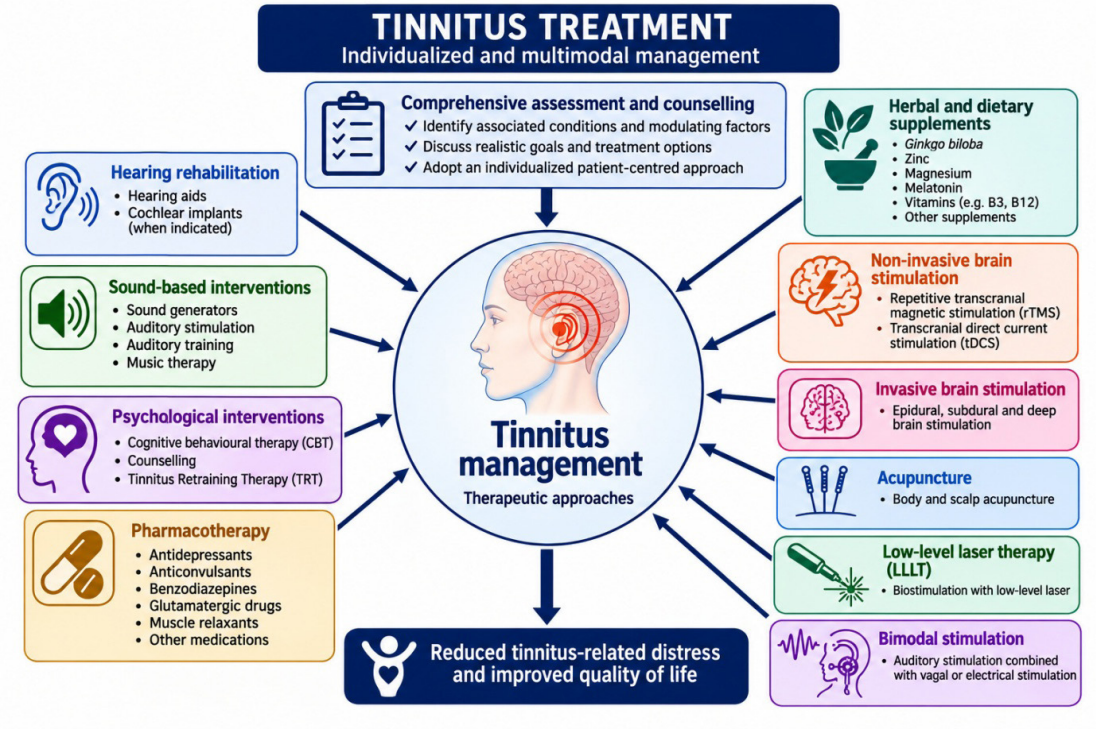

Figure 4. Tinnitus treatment options

Tinnitus Retraining Therapy (TRT) combines counselling and sound therapy based on a neurophysiological model and has been associated with improved subjective tinnitus outcomes, although the independent contribution of sound therapy remains debated [47].

Cognitive behavioral therapy (CBT) is a structured psychological intervention that addresses unhelpful thoughts and behaviours associated with tinnitus and aims to reduce distress by modifying maladaptive interpretations and responses [48]. CBT is based on the idea that the way we perceive situations affects how we feel and that we have the ability to change our thinking patterns to feel better by changing our perceptions.

Auditory interventions can be divided into four categories: devices for improving hearing, sound generators for tinnitus masking, auditory stimulation to induce specific neuroplastic changes in the central auditory system and auditory training. Hearing aids are recommended for patients with hearing loss and tinnitus because they improve speech audibility and increase access to ambient sound, which may reduce tinnitus prominence. Sound therapy uses external sound for masking or other therapeutic purposes, while auditory training targets skills such as frequency discrimination,

sound localization, or speech-in-noise perception [46]. The Heidelberg music therapy model is one extensively investigated approach. Music therapy is also one of the treatment options. Extensively investigated model is the Heidelberg model consisting of nine individualized therapy sessions.

Non-invasive brain stimulation includes transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). They consist of delivering a weak direct current to the head electrodes and using devices that generate short magnetic pulses. These approaches have shown potential benefits, although their clinical effectiveness remains under investigation.

Neurofeedback is a non-invasive neuromodulation technique that records neuronal activity, extracts relevant aspects of brain processes through real-time signal processing, and returns feedback to the individual as visual or auditory stimuli. The goal of neurofeedback is to change behavior or medical conditions associated with altered neuronal activity, such as chronic tinnitus. This is generally done through operant conditioning.

Invasive brain stimulation represents a highly experimental treatment requiring surgical insertion of electrodes under the skull. Epidural, subdural and deep brain stimulation has shown potential benefit mainly in case series [46].

Bimodal stimulation combines auditory stimulation with somatosensory or other electrical stimulation to promote neuroplastic changes and has been investigated in several forms. One involves the presentation of tones in combination with vagal nerve stimulation via an implanted vagus nerve stimulation device. There is also an auditory stimulation in the form of short "notched noise" bursts customized to each participant's tinnitus percept. Simultaneous pulsed electrical stimulation, intended to facilitate neuroplasticity, was delivered via hydrogel electrodes placed in opposite ears [49].

Low-level laser therapy (LLLT) has been investigated as a biostimulation approach for tinnitus, although its clinical role remains uncertain.

Acupuncture is a therapeutic method that involves the insertion of needles into the acupuncture points on the body. Scalp acupuncture is widely used in Asian countries. There is not enough evidence to recommend or reject this treatment [50].

DISCUSSION

Tinnitus is a heterogeneous condition involving interactions between peripheral auditory abnormalities, central neural plasticity, and networks related to attention, cognition, emotion, and autonomic regulation. Although hearing loss is the most consistently recognized associated factor, tinnitus may also occur with normal conventional thresholds, reflecting the limitations of routine audiometry and the possible contribution of cochlear synaptopathy or other subclinical abnormalities.

No single pathophysiological theory adequately explains all clinical presentations. Current evidence supports a network-based, multidimensional model in which abnormal auditory activity interacts with cognitive, emotional, autonomic, behavioral, and environmental factors, helping explain individual differences in perception, distress, and functional impact.

Consequently, tinnitus assessment should extend beyond identifying an auditory abnormality to include tinnitus characteristics, hearing function, psychological impact, sleep, and daily functioning. Management should be individualized; auditory rehabilitation, sound-based interventions, TRT, and CBT remain important, while neuromodulatory and other emerging approaches require further evidence regarding long-term clinical value.

CONCLUSION

Tinnitus is a common and clinically heterogeneous condition arising from interactions between auditory and non-auditory systems. Its perception and impact are influenced by biological, audiological, psychological, lifestyle, and environmental factors. Comprehensive assessment and individualized, multidisciplinary management are therefore essential. Although no universal treatment exists, advances in understanding tinnitus mechanisms and its multidimensional nature provide a basis for increasingly approaches to treatment.

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NONOPERATIVE MANAGEMENT OF CECAL DIVERTICULITIS PRESENTING AS ACUTE APPENDICITIS: A CASE REPORT

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ABSTRACT

Cecal diverticulitis is an uncommon condition that may closely mimic acute appendicitis due to similar clinical presentation. We report the case of a 39-year-old female presenting with right lower quadrant abdominal pain, nausea, and elevated inflammatory markers. Computed tomography revealed cecal wall thickening, pericecal fat stranding, and an inflamed diverticulum, along with a mildly dilated appendix, without evidence of perforation or abscess. Given the absence of complications and stable clinical condition, conservative management with antibiotics and supportive care was initiated. The patient showed favorable clinical evolution and was discharged without surgical intervention. This case highlights the diagnostic challenge posed by cecal diverticulitis and supports the role of imaging in guiding appropriate, nonoperative management.

Key words : diverticulosis, cecal diverticulitis, appendicitis.

INTRODUCTION

Diverticulosis is characterized by the development of mucosal outpouchings within the colonic wall, which may become inflamed, resulting in diverticulitis. Cecal diverticulitis represents an uncommon clinical entity and may closely mimic acute appendicitis due to overlapping clinical and radiological features. The optimal management strategy remains a matter of debate, ranging from conservative medical therapy to surgical intervention. We herein report a case of cecal diverticulitis successfully managed with a nonoperative approach.

AIM

The aim of this report is to contribute to the existing clinical evidence on cecal diverticulitis by describing its presentation as a diagnostic challenge due to its resemblance to Acute appendicitis, and to illustrate the clinical decision-making process in selecting an appropriate management strategy.

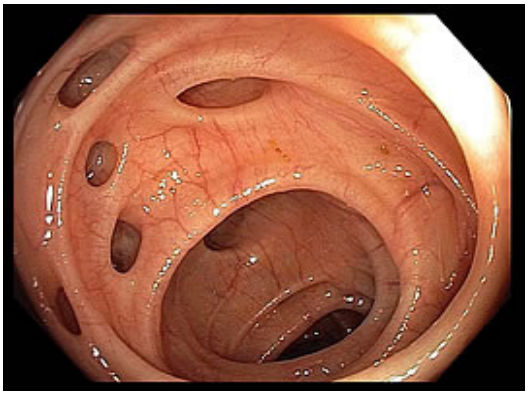
CASE REPORT

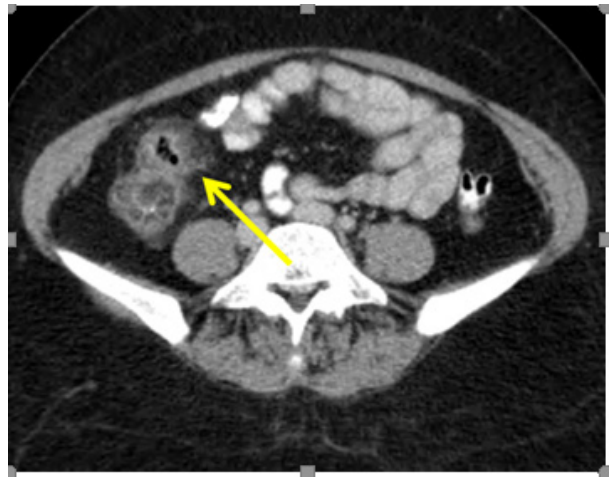
A 39-year-old female was admitted with a three-day history of lower abdominal pain accompanied by nausea and

tachycardia. The patient was subfebrile and denied any alterations in bowel habits. Physical examination revealed rebound tenderness localized to the right lower quadrant, with concomitant elevation of inflammatory markers. Computed tomography of the abdomen demonstrated focal thickening of the cecal wall, associated with pericecal fat stranding and localized edema, as well as a possible small fluid collection. A hyperdense diverticulum within the cecum and multiple non-inflamed diverticula in the ascending colon were identified. The appendix was noted to be mildly dilated (8mm) with surrounding fat stranding. No radiological evidence of perforation or abscess formation was observed.

Test	Value	Normal Range	Unit
WBC	12	4.0–11.0	$\times 10^9$/L
HGB	125	120–160 (♀) / 130–180 (♂)	g/L
CRP	196	<5	mg/L
PLT	378	150–400	$\times 10^9$/L
RBC	4.5	4.2–5.4 (♀) / 4.7–6.1 (♂)	$\times 10^{12}$/L

In the absence of complications and given the patient's stable clinical status, a conservative management strategy was pursued, consisting of antibiotic therapy, intravenous hydration, analgesia, and close clinical observation. A cardiologist was also consulted. The patient demonstrated favorable clinical evolution and was discharged without the need for surgical intervention.





Cecal diverticulitis may present with clinical and imaging findings indistinguishable from acute appendicitis, thereby posing a diagnostic challenge. This case emphasizes the importance of meticulous diagnostic evaluation in order to establish an accurate diagnosis and guide appropriate management.

DISCUSSION

Cecal diverticulitis represents a relatively uncommon form of right-sided colonic diverticular disease, particularly in Western populations, where diverticulitis more frequently involves the sigmoid colon. Its clinical significance lies in its frequent misdiagnosis as acute appendicitis, owing to the similarity in presentation, including right lower quadrant abdominal pain, fever, and leukocytosis. As demonstrated in the present case, this overlap may lead to diagnostic uncertainty and potentially unnecessary surgical intervention.

The pathogenesis of cecal diverticula differs from that of left-sided diverticula. Right-sided diverticula are often considered congenital and true diverticula, involving all layers of the bowel wall, whereas left-sided diverticula are typically acquired pseudodiverticula. Although frequently asymptomatic, inflammation of a cecal diverticulum can result in localized peritonism, further mimicking appendicitis. In the absence of advanced imaging, the distinction between these entities based solely on clinical evaluation remains challenging.

In this context, computed tomography has emerged as the diagnostic modality of choice. CT imaging not only facilitates differentiation between cecal diverticulitis and acute appendicitis but also allows for the assessment of disease severity and the identification of complications

such as perforation, abscess formation, or phlegmon. Typical CT findings of cecal diverticulitis include focal cecal wall thickening, pericecal fat stranding, and the presence of an inflamed diverticulum, whereas visualization of a normal or only mildly reactive appendix supports the diagnosis. In the present case, CT imaging played a pivotal role in establishing the diagnosis and guiding management.

The optimal management of cecal diverticulitis remains a subject of ongoing debate. Historically, surgical intervention, including appendectomy or right hemicolectomy, was commonly performed due to diagnostic uncertainty and concern for malignancy. However, increasing evidence supports conservative management in uncomplicated cases. Nonoperative treatment, consisting of antibiotic therapy, bowel rest, and supportive care, has been shown to be both safe and effective in carefully selected patients without signs of generalized peritonitis or sepsis.

The present case supports this evolving paradigm, as the patient was successfully managed with a conservative approach, resulting in complete clinical resolution without the need for surgical intervention. This approach not only reduces the risks associated with surgery but also shortens hospital stay and recovery time. Nevertheless, careful patient selection and close clinical monitoring remain essential, as delayed recognition of complications may adversely affect outcomes.

Furthermore, follow-up evaluation is recommended after resolution of the acute episode to exclude underlying malignancy or other colonic pathology, particularly in cases with atypical imaging findings or incomplete clinical resolution. Colonoscopic assessment is often advised once the acute inflammation has subsided.

CONCLUSION

In conclusion, cecal diverticulitis should be considered in the differential diagnosis of right lower quadrant abdominal pain. Accurate diagnosis, primarily through CT imaging, is crucial in order to distinguish it from acute appendicitis and to guide appropriate management. In the absence of complications, conservative treatment represents a safe and effective therapeutic option, as illustrated by the present case.

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"ENDOBRONCHIAL ANTHRACOSIS MIMICKING MALIGNANCY IN A PATIENT WITH SEVERE BILATERAL PNEUMONIA: A CASE REPORT"

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ABSTRACT

Background: Endobronchial anthracosis is characterized by black pigmentation of the bronchial mucosa due to the deposition of carbon particles. It may clinically and radiologically resemble malignancy, especially in elderly patients presenting with obstructive features and persistent consolidations. Case Presentation: We report a case of a 76-year-old non-smoking male from the Pollog region who presented with progressive dyspnea and productive cough. Laboratory findings showed elevated inflammatory markers (CRP 81.8 mg/L; ESR 65 mm/h). Contrast-enhanced chest CT revealed extensive bilateral interstitial and alveolar consolidations (right > left), with partial right-sided atelectasis. Bronchoscopy demonstrated edematous mucosa, abundant purulent secretions, and a pigmented endobronchial lesion. Bronchial aspirate grew Streptococcus beta-hemolyticus, which was sensitive to multiple antibiotics. Histopathological analysis of bronchial biopsies confirmed anthracotic pigment deposition without malignancy. Clinical and radiological improvement was observed following antibiotic therapy. Conclusion: This case highlights the diagnostic challenge of differentiating severe pneumonia from endobronchial malignancy in elderly patients and emphasizes the importance of histopathological confirmation in suspected anthracotic lesions. Early use of bronchoscopy and biopsy is essential to avoid misdiagnosis and inappropriate management.
Keywords: Endobronchial anthracosis; Bilateral pneumonia; Atelectasis; Bronchoscopy; Pollog region; Biomass exposure

INTRODUCTION

Anthracosis is characterized by the deposition of carbon pigment in the bronchial mucosa, typically as a result of chronic exposure to biomass smoke, air pollution, or occupational inhalants [1,2]. When associated with bronchial narrowing and fibrosis, it is referred to as anthracofibrosis [3]. Although often considered benign, anthracosis can present with a variety of symptoms, including cough, dyspnea, radiologic consolidations, atelectasis, and endobronchial lesions, which may mimic lung cancer [4–6]. In areas with significant environmental pollution and high biomass exposure, such as parts of the Balkans, chronic inflammatory changes in the airways are often underrecognized [7].

The challenge of differentiating infectious consolidation from obstructive or neoplastic pathology remains particularly difficult in elderly patients. Notably, the diagnosis of anthracosis is usually first suspected through bronchoscopy, with confirmation made by histopathological examination via biopsy. This emphasizes the crucial role of invasive diagnostic procedures in achieving a definitive diagnosis. Despite its importance, there remains a limited number of reports that combine severe bilateral pneumonia with

endobronchial anthracosis that mimics malignancy in the literature.

In this report, we present a case of histologically confirmed endobronchial anthracosis in a 76-year-old patient who presented with severe bilateral pneumonia and radiologic findings suspicious for malignancy in a city of approximately 250,000 inhabitants. This case is noteworthy as it is documented as the first such occurrence in the clinical records of the Tetovo Clinical Hospital, marking a significant contribution to the understanding of anthracosis in the region.

Case Presentation: A 76-year-old male from the Pollog region was admitted with progressive dyspnea, a persistent productive cough with thick sputum, and clinical deterioration over several weeks. He denied smoking, alcohol consumption, and illicit drug use. He had worked for approximately 40 years in the hospitality sector and reported long-term exposure to biomass fuel and indoor smoke earlier in life. No significant family history of pulmonary malignancy was noted. Upon admission, vital parameters were stable: Blood pressure: 129/66 mmHg , Heart rate: 96/min, Oxygen saturation: 99% ,Afebrile. Auscultation revealed bilateral crackles, more pronounced on the right side.

Laboratory Findings: Initial laboratory analysis showed: CRP: 81.8 mg/L ,ESR: 65 mm/h,Follow-up testing (9 days later) demonstrated: CRP: 70.4 mg/L, ESR: 66 mm/h .These findings were consistent with an active but partially regressing inflammatory process.

Radiological Findings: Contrast-enhanced chest CT (13.01.2026) demonstrated:

Multiple small nodular opacities in the right lung

Apical and middle lobe solid parenchymal consolidations with air bronchogram

Bilateral interstitial and alveolar consolidations (right side more extensive)

Partial right-sided atelectasis with mild mediastinal shift

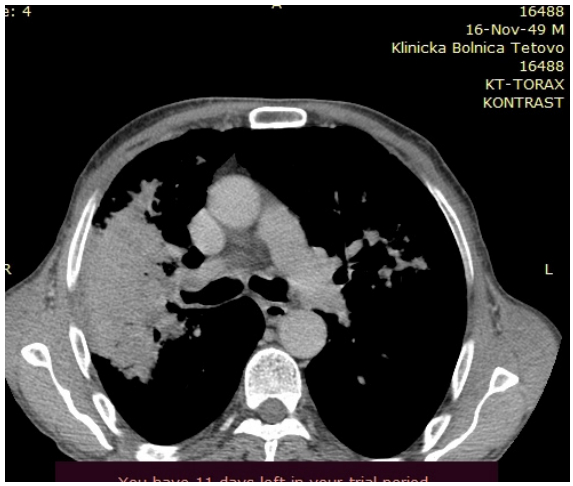
No pleural effusion

No significant mediastinal, hilar, or axillary lymphadenopathy

Mild cardiomegaly

Follow-up CT (22.01.2026) showed mild-to-moderate regression of consolidations but persistent significant parenchymal abnormalities. These findings raised suspicion of severe bilateral pneumonia with a possible underlying obstructive or neoplastic process.

FIGURE 1 – INSERT HERE (CT IMAGES)



CT – axial

Figure 1: Contrast-enhanced chest CT showing bilateral alveolar and interstitial consolidations (predominantly right side) with partial right-sided atelectasis and air bronchogram.

- Bronchoscopy and Microbiology. Flexible bronchoscopy revealed:
- Edematous trachea with nodular changes
- Right bronchus filled with thick whitish purulent secretions
- Mucosal discoloration and fragility at the entrance of the lower medial bronchus
- Black pigmented endobronchial plaques partially covering the lesion
- No active bleeding

Bronchial lavage was performed bilaterally.

FIGURE 2 – INSERT HERE (BRONCHOSCOPY IMAGE)

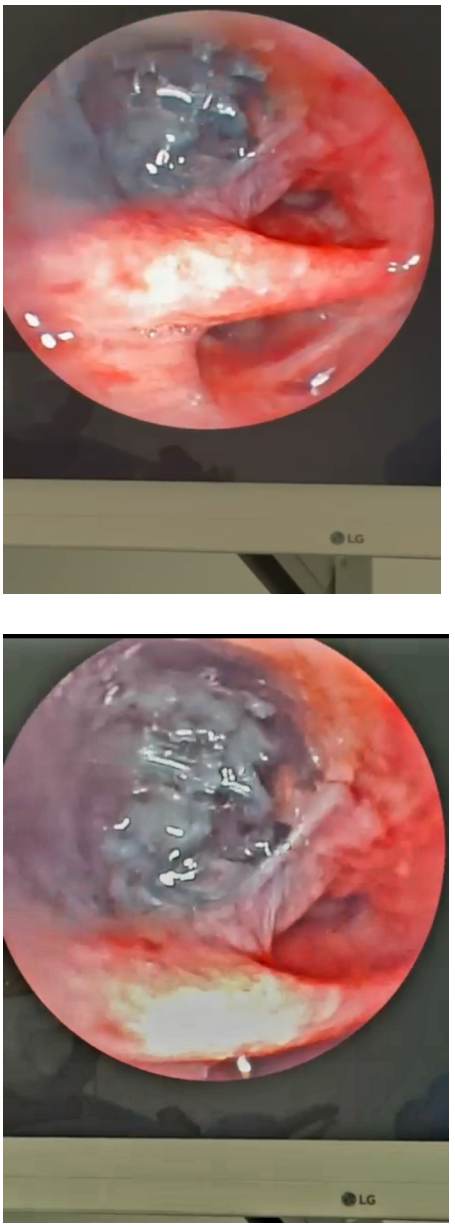


Figure 2: Bronchoscopic view demonstrating black pigmented endobronchial lesions consistent with anthracosis, associated with mucosal edema and purulent secretions.

Microbiological analysis of the bronchial aspirate identified Streptococcus beta-hemolyticus, which was sensitive to: Ampicillin, Amoxicillin, Amoxicillin-clavulanic acid, Ceftriaxone, Macrolides, Clindamycin

Histopathology: Bronchial biopsy specimens demonstrated:

- Carbon pigment deposition within the bronchial mucosa and submucosa
- Chronic inflammatory infiltrate
- Absence of dysplasia or malignant cells

These findings were diagnostic for endobronchial anthracosis.

FIGURE 3 – INSERT HERE (HISTOPATHOLOGY IMAGE)

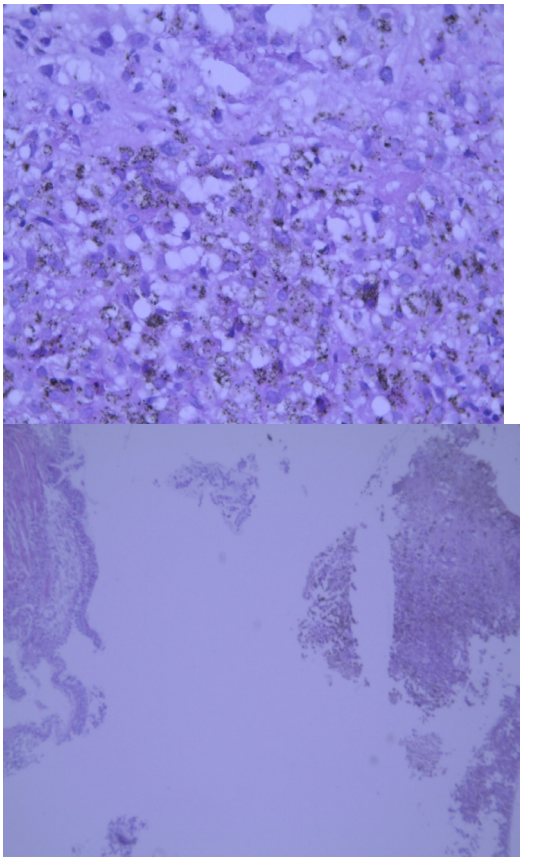


Figure 3: Histopathological examination showing carbon pigment deposition within the bronchial mucosa and submucosa with chronic inflammatory infiltrate (H&E stain, magnification ×100/×200).

Treatment and Outcome

The patient was treated with intravenous ceftriaxone (2 g twice daily). Vancomycin was initially administered empirically and later reconsidered based on microbiological sensitivity. Clinical improvement was observed with a gradual reduction in inflammatory markers and partial radiologic regression of consolidations. Given the histological confirmation of anthracosis and the absence of malignancy, no oncologic treatment was required. The patient was discharged with a pulmonology follow-up and a recommendation for repeat imaging after 6–8 weeks.

DISCUSSION

Anthracosis is increasingly recognized as a

benign but diagnostically challenging condition [1,4]. It may present with bronchial narrowing, atelectasis, and persistent consolidations, which can raise suspicion of malignancy [5,8]. Several studies report a strong association between anthracosis and biomass smoke exposure, even in non-smokers [2,9]. Chronic environmental pollution may contribute to carbon deposition and bronchial inflammation [7,10]. Radiologically, anthracosis may manifest as segmental atelectasis, lymphadenopathy, or parenchymal consolidation [6,11]. Bronchoscopy typically reveals black pigmentation, while histopathology confirms carbon-laden macrophages without malignant transformation [3,12]. An important consideration is that anthracosis may coexist with infectious processes, further complicating clinical and radiologic interpretation, as demonstrated in this case. In this case, severe bilateral pneumonia coexisted with anthracotic bronchial changes. The partial atelectasis was likely the result of inflammatory obstruction rather than a tumor. Histopathological confirmation was crucial in excluding lung cancer. Differentiating anthracosis from malignancy remains essential, particularly in elderly patients with persistent radiologic abnormalities [13–15].

CONCLUSION

Endobronchial anthracosis should be considered in elderly patients presenting with suspicious bronchial lesions and persistent consolidations, particularly in regions with environmental pollution exposure. Histopathological examination remains mandatory to exclude malignancy and guide management. This case underscores the importance of comprehensive diagnostic evaluation integrating imaging, bronchoscopy, microbiology, and histopathology. Early use of bronchoscopy and biopsy is essential to avoid misdiagnosis and inappropriate management.

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SALIVARY GLAND ADENOID CYSTIC CARCINOMA: CASE REPORT

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ABSTRACT

Adenoid cystic carcinoma (AdCC) is a rare carcinoma of unknown etiology, originating from the secretory glands. It is one of the most dominant malignant salivary tumors. It occurs across all age groups, but is more prevalent between the ages of 50 and 70, and is more common in women than in men. It is a slowly growing aggressive tumor, characterized by perineural invasion and late metastases. The symptoms of AdCC are generally nonspecific, and the clinical diagnosis of AdCC can be challenging, partly due to its heterogeneous histopathology and its indolent growth. Due to its rarity, it is difficult to predict which therapeutic methods are most optimal, especially given the occurrence of many late recurrences. In this paper, we present our clinical experience in the treatment of this carcinoma, accompanied by a case presentation. The case order encompasses preoperative planning, the surgical intervention, and postoperative monitoring and oncological treatment.

Keywords : salivary gland; adenoid cystic carcinoma;case report

INTRODUCTION

Adenoid cystic carcinoma (AdCC) is a rare type of malignancy with an as yet unknown etiology that originates from the secretory glands (1). Specifically, it is one of the most common malignant salivary tumors, accounting for approximately 10% of all tumors in the major salivary glands and 30% of all tumors in the minor salivary glands (2). However, its occurrence is not limited solely to the salivary glands, but also extends to other locations in the head and neck region, as well as in secretory glands outside of the head and neck area, such as in the esophagus, chest, and lungs. It can manifest at all ages, but is most prevalent in the fifth or sixth decade of life, with approximately 60-70% of patients being women (3).

AdCC manifests with nonspecific symptoms, making clinical differentiation from benign tumors challenging. It is characterized by slow growth and perineural invasion, and in many cases, it poses a difficult differential diagnosis due to the lack of reliable diagnostic markers (4).

Clinically, AdCC typically manifests as a painless, slowly growing tumor mass and may often remain asymptomatic until it induces neurological deficits due to perineural spread. These factors contribute to its late diagnosis, and its biological characteristics complicate long-term management (5,6). Even with extensive surgical resection and adjuvant radiotherapy, recurrences are a frequent occurrence. This phenomenon is largely attributed to the subclinical dissemination of the tumor within the nerve sheaths and vascular pathways, which undermines the

efficacy of standard local therapies (7).

The primary treatment consists of radical surgical intervention, often accompanied by adjuvant radiotherapy. However, despite the aggressive treatment regimen, late recurrences (15-85%) and distant metastases (25-55%) are common, particularly manifesting late, beyond five years or even more than ten to fifteen years after the completion of the primary treatment. It is presumed that this phenomenon arises from perineural invasion beyond surgical margins and microscopic hematogenous dissemination during the early phase of the disease. Due to the slow growth and indolent clinical course of AdCC, the five-year survival rates are 80-85%; however, the ten- and fifteen-year survival rates decline to 50-60%.

In this paper, we present our clinical experience in the treatment of this carcinoma, accompanied by a case presentation. In accordance with the ethical principles of research involving human subjects and the Helsinki Declaration, written informed consent for the case study was obtained from the patient.

CASE PRESENTATION

History of the patient and clinical findings

A 68-year-old female patient presented for examination at the Department of Maxillofacial Surgery, Clinical Hospital Štip, in December 2024, having been referred by her primary care physician due to paresis of the right facial nerve. Several months prior, the patient had been referred by a neurologist for physical therapy and treated by a physiotherapist due to suspicion of a cerebral stroke, which resulted in left-sided facial paresis.

Diagnostic Assessment

During the initial clinical examination, left-sided facial paresis was detected, characterized by an inability to wrinkle the forehead, an inability to close the left eye, and a depressed left corner of the mouth. In the left parotid region, a tumor formation was palpated, immobile, painless, and approximately the size of a mandarin.

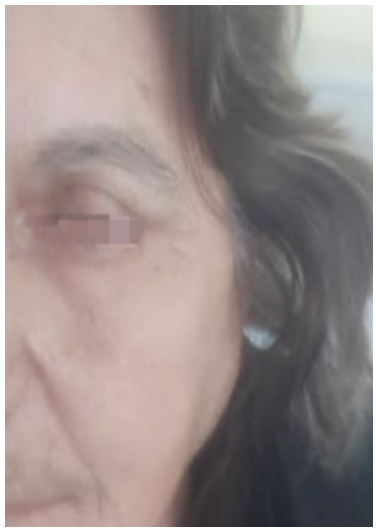

Figure 1

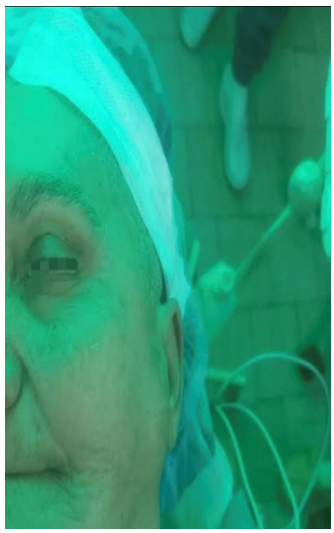

Figure 2

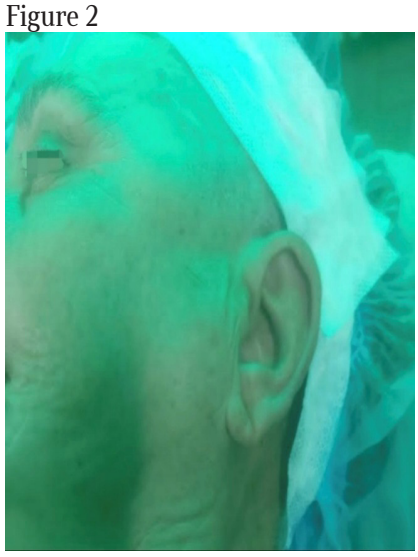

Figure 3

Figure 1, 2, 3, - The preoperative condition of the patient

The ultrasound sonography conducted has revealed the presence of a tumor mass in the left parotid gland. A fine needle aspiration biopsy (FNAB) was performed, resulting in a diagnosis of adenoid cystic carcinoma. A CT scan of the head with contrast was carried out, during which the tumor formation was visualized, yet no focal lesions were noted within the cerebral structures.

Surgical Intervention

An indication for surgical treatment was established. The operation was performed in the operating room. A radical excision of the tumor was conducted, along with the complete removal of the parotid gland (total parotidectomy), with identification and preservation of the intact portion of the facial nerve. An active Redon drain was placed.

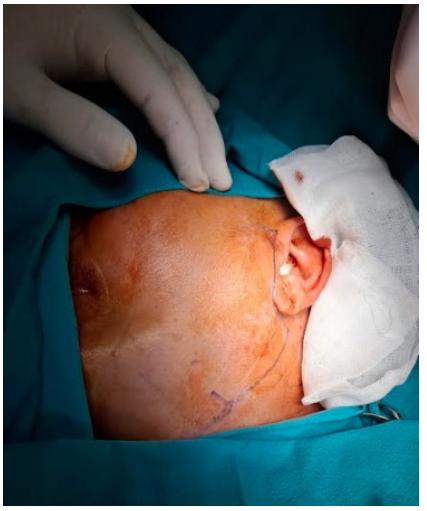

Figure 4

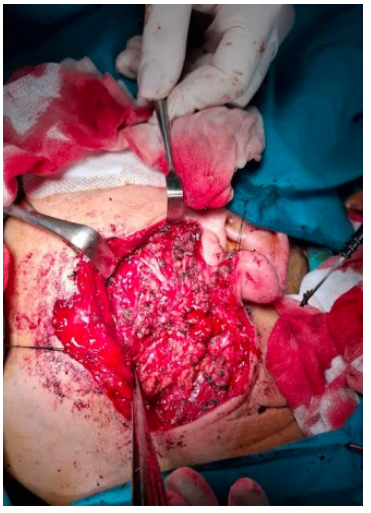

Figure 5

Figure 6

Figure 4,5,6 Surgical Intervention and Intraoperative Findings

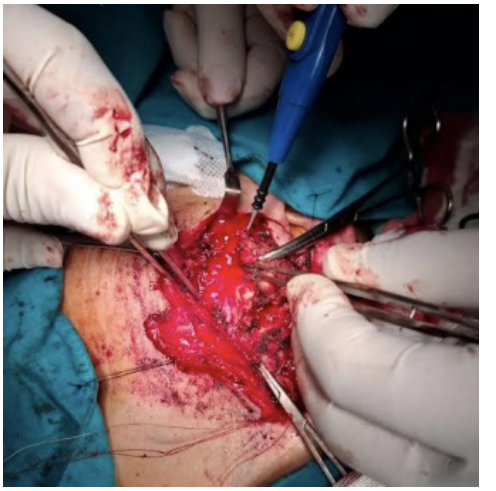

Figure 7 Branches facialis

Postoperative course and outcomes

Postoperatively, the patient was treated at the Oncology Clinic with radiotherapy. Regular follow-up examinations were conducted one month postoperatively (during the first six months) and every three months thereafter. At six and twelve months postoperatively and post-radiation, a CT scan of the head was performed. No recurrences or regional metastases were observed. During the follow-up examinations, moderate left-sided facial paresis remains present. Following the last examination in June 2026, the patient was referred to the Department of Physical Medicine and Rehabilitation for treatment of the residual facial paresis.

CONCLUSIONS

AdCC represents rare carcinomas, and the limited number of studies with larger cohorts complicates the extraction of general conclusions. AdCC is an uncommon disease, primarily affecting the middle-aged population, and is more prevalent among women than men. In the region of the head and neck, it affects both the minor and major salivary glands. Its diagnosis is not always straightforward, and distinguishing it from benign tumors or other types of tumors presents a clinical challenge. According to some studies (8,9,10,11,12) among patients with AdCC in the head and neck region, the prognosis has been better for those with tumors arising from major salivary glands compared to those with tumors originating from minor salivary glands. Patients with stage I-II of the disease generally exhibited better outcomes than those with stage III-IV, while gender, smoking, and age typically did not influence the results. Multimodal therapy proved superior to monotherapy, regardless of radical surgery or perineural invasion. However, there is no plateau in the survival curves, and therefore, a longer follow-up period for these patients is recommended. Consequently, based on current data, we propose that AdCC receive multimodal treatment, and the follow-up should extend beyond 5 years, as no plateau in the survival curves is observed after 15 years of monitoring.

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DIAGNOSIS OF LATENT AUTOIMUNE DIABETES IN ADULTS (LADA) IN PATIENT INITIALLY TREATED AS TYPE 2 DIABETES MELLITUS - A CASE REPORT

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ABSTRACT

Latent autoimmune diabetes in adults (LADA) is a slow progressive autoimmune destruction of pancreatic beta cells. This condition tends to manifest during adulthood, often around 30 years of age. While LADA can initially be managed by oral medications, eventually the patient will require insulin. LADA is frequently misdiagnosed as Type 2 Diabetes due to its gradual onset and initial response to oral therapy. Early recognition is critical to optimize glycemic control and prevent long term complications.

We present a 58-year-old female patient with a 10-year history of diabetes treated with oral therapy including Metformin and Sulfonylurea. Despite therapy, the patient exhibited persistently poor glycemic control. The patient also has been diagnosed with autoimmune thyroiditis for which she was in therapy with levothyroxine a 100mcg. Anthropometry and laboratory tests were as follows: low body mass index (BMI), basal and postprandial glycemia = 12. 8mmol.L, and 19mmol/L respectively, glycated, HbA1C above 10%. Immunological tests showed significantly elevated levels of Glutamic Acid Decarboxylase Antibody (GAD) at 1288 IU/ml and positive Islet Cell Antibody at 52.4 IU/ml, confirming the diagnosis of LADA. While Insulin Autoantibody and IA-2 Antibody were negative. Family history revealed a first-degree relative (mother and father) with type 2 diabetes mellitus.

During hospitalization, the patient was transitioned to an intensive insulin with basal-bolus therapy, resulting in significant improvement in glycemic control.

Keywords: Latent autoimmune diabetes mellitus in adults, Type 1and 2 Diabetes Mellitus, Anti-glutamic acid decarboxylase autoantibody (anti-GAD), Non-insulin requiring autoimmune diabetes, Slowly-progressing type 1 diabetes.

INTRODUCTION

Latent autoimmune diabetes in adults (LADA) is estimated to account for 2–14% of all cases of diabetes in adults.1.2 Often misdiagnosed as type 2 diabetes mellitus (T2DM), it causes inefficient and delayed glycemic control leading to enhanced diabetes-related mortality and morbidity.3

According to the Immunology of Diabetes Society's criteria to diagnose LADA,5 the patient should be: (a) aged ≥ 30 years; (b) positive for at least one of the four antibodies commonly seen in T1DM, namely islet cell antibodies, anti-glutamic acid decarboxylase (GAD) autoantibodies, insulinoma associated-2 autoantibodies, and insulin autoantibodies; and (c) free of insulin treatment for the

first six months after the initial diagnosis.

On initial presentation, especially in young adults, it is important to consider the possibility of LADA and know how to distinguish its symptoms and history from those of T1DM and T2DM [Table 1].

Table 1. Comparative characteristics of type 1 diabetes mellitus (T1DM), latent autoimmune diabetes in adults (LADA), and type 2 diabetes mellitus (T2DM).6

Characteristics	T1DM	LADA	T2DM
Age of onset	Childhood or Adulthood	Adulthood	Adulthood
Metabolic syndrome	Similar to the general population	Similar to the general population	Present in 80-90% of cases
Ketoacidosis	Frequent	Infrequent	Late
Autoimmunity	Present (ICA predominates)	Present (anti-GAD predominates)	Absent
Insulin therapy	Since the diagnosis	Not required for about six months	Late

ICA : islet cell autoantibodies; GAD: glutamic acid decarboxylase.

However, the above criteria turned out to be insufficient to diagnose LADA. This is because LADA is a multiplex disorder with a few patients manifesting high antibody titers, lower body mass index (BMI), and progressing rapidly to insulin requirement, while others have low antibody titers with features of insulin resistance such as higher BMI and progress more slowly to insulin requirement.3 LADA with high BMI is also referred to as 'double diabetes', and these patients are also likely to have a family history of T2DM with or without the clinical features of insulin resistance.7

In a retrospective study, Fourlanos et al,8 proposed a five-point LADA clinical screening tool consisting of (a) age at onset < 50 years; (b) acute symptoms; (c) BMI < 25 kg/m2; (d) a history of autoimmune disease; and (e) a family history of diabetes. This tool had a sensitivity of 90% and specificity of 71% in identifying LADA patients if they had at least two of the five clinical features. In cases where only one or none of these features were present, a negative predictive value of 99% was given.8

This case report presents a 58 year old female patient initially treated as Type 2 Diabetes Mellitus, whose persistent hyperglycemia and positive autoantibody profile led to the diagnosis of LADA, highlighting the importance of considering autoimmune diabetes in adult patients with poor metabolic control.

CASE PRESENTATION

A 58-year-old female presented to the University Clinic of Endocrinology unit for glycemic regulation and further diagnostic evaluation, due to long-standing poorly controlled diabetes mellitus. At presentation, capillary and plasma glucose measurements revealed marked postprandial hyperglycemia of up to 27 mmol/L, accompanied by positive urinary ketones, indicating significant metabolic instability and evolving insulin deficiency. The patient reported a prolonged history of classical hyperglycemic symptoms, including progressive polyuria, polydipsia, generalized fatigue, and unintended weight loss, which had been present for several years but had markedly worsened in the months preceding admission. There was no history of acute infection, corticosteroid exposure, or other secondary causes of hyperglycemia. The indication for hospitalization was severe hyperglycemia refractory to oral antidiabetic therapy, with documented HbA1c values persistently exceeding 10%.

The patient had been diagnosed in 2017, with diabetes mellitus, classified at that time as type 2 diabetes mellitus, based on adult age at onset and absence of ketoacidosis. At diagnosis, HbA1c was 9.0%, indicating chronic hyperglycemia. Concomitantly, during the same endocrine evaluation, the patient was diagnosed with primary hypothyroidism. This diagnosis was established based on: elevated serum TSH levels, abnormal free and thyroxine (fT4) concentrations and characteristic findings on thyroid ultrasonography. Both conditions were identified concurrently during the initial endocrine evaluation.

Initial pharmacological management included: Metformin 500mg twice daily, Levothyroxine 50mcg once daily.

By 2020, owing to persistent hyperglycemia (HbA1c 10%), the metformin dosage was escalated to 1000mg twice daily.

In 2022, ambulatory follow-up revealed further deterioration of glycemic control (HbA1c 11.6%), prompting intensification of therapy with: Metformin 850mg twice daily, Glimepiride (Amaryl) 1mg once daily. Over the subsequent four years, the patent resided abroad and adhered inconsistently to therapy, without structured

medical follow-up or laboratory monitoring. The most frequently used regimen consisted of glimepiride 1mg and metformin 1000mg.

Family and Personal History

The patient reported a positive family history of diabetes mellitus, with both parents diagnosed with type 2 diabetes and treated with oral antidiabetic agents. Additionally, she had a known diagnosis of autoimmune thyroid disease, strengthening the suspicion of an autoimmune predisposition.

She was an active smoker, with an estimated tobacco exposure of approximately 20 cigarettes per day. There was no history of alcohol abuse or illicit drug use.

Physical Examination

On admission, the patient was conscious, oriented and cooperative, lying comfortably ind bed. She appeared underweight, with no signs of acute distress.

Body weight: 45kg

Height: 155cm

BMI: 18.75 kg/m2

Blood pressure and heart rate were within normal limits. No clinical signs of diabetic neuropathy or macrovascular complications were noted at presentation.

Laboratory Findings

Table 2. Laboratory parameters during hospitalization:

Parameter	Result	Reference Range
HbA1c	14%	<5.7 %
Fasting plasma glucose	24 mmol/L	3.89-6.11 mmol/L
Insulin	0.5 mIU/L	3-17 mIU/L
C-peptide	1.38 ng/ml	1.1-4.4 ng/mL
TSH	5.5 mIU/L	0.4-4.0 mIU/L
fT4	Decreased	9.5-25pmol/L
Anti-TPO	403 IU/mL	<35 IU/mL
Creatinine (s)	60 umol/L	45-90 umol/L
Urea	4.87 mmol/L	2.9-8.2 mmol/L
Total cholesterol	5.45 mmol/L	<5.2 mmol/L
LDL cholesterol	3.3 mmol/L	2-3.1 mmol/L
HDL cholesterol	1.71 mmol/L	0.70-1.70 mmol/L
Triglycerides	1.26 mmol/L	<1.7 mmol/L
CRP	0.2 mg/L	<3 mg/L
Proteinuria	<0.1 g/day	<0.15 g/L
eGFR	101mL/min/1.73m2	>90

Findings were consistent with significant endogenous insulin deficiency, poor glycemic control, preserved renal function and active autoimmune hypothyroidism.

Hospitalization and Management

The patient was hospitalized for six day at the University Clinic of Endocrinology, Skopje, due to marked hyperglycemia and metabolic decompensation. All oral antidiabetic agents were discontinued, and intensive insulin therapy was initiated using a basal-bolus regimen:

Insulin glargine (Lantus) 14 IU s.c at bedtime

Insulin glulisine (Apidra) 6+6+6 IU s.c before meals

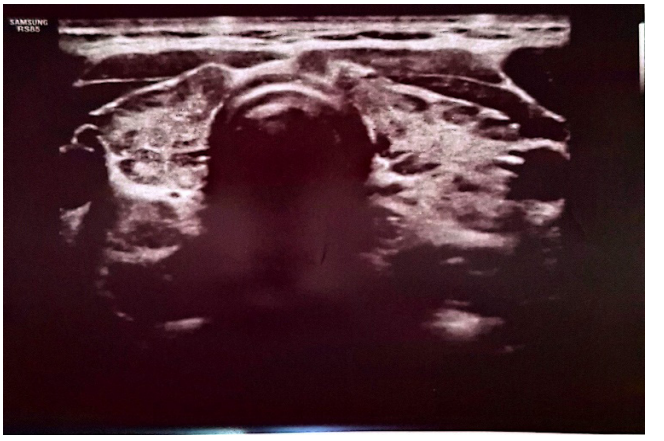
During hospitalization, serial glycemic profiling was performed (table 3), and insulin doses were titrated accordingly (Ins. Lantus 28 IU s.c, Ins. Apidra 12+12+12 IU s.c)

Table 3. Daily glycemic profile during early hospitalization

	07:00h	13:00h	18:00h	22:00h
Day 1:		15.5 mmol/L	10.2 mmol/L	18 mmol/L
Day 2:	12.8 mmol/L	19.6 mmol/L	14.8 mmol/L	9 mmol/L
Day 3:	11.4 mmol/L	6.3 mmol/L	17.7 mmol/L	6.3 mmol/L
Day 4:	9.0 mmol/L	7.1 mmol/L	11.9 mmol/L	9.4 mmol/L
Day 5:	8.8 mmol/L	7.9 mmol/L	12.3 mmol/L	8.6 mmol/L
Day 6:	8.6 mmol/L	7.5 mmol/L	11.3 mmol/L	8.0 mmol/L

These profiles demonstrated marked glycemic variability, with significant postprandial excursions, supporting the diagnosis od advanced β-cell failure.

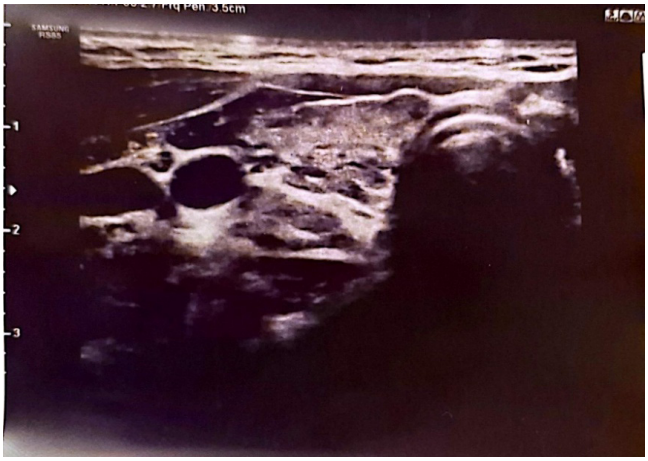
Imaging and Additional Investigations



(Fig.1)

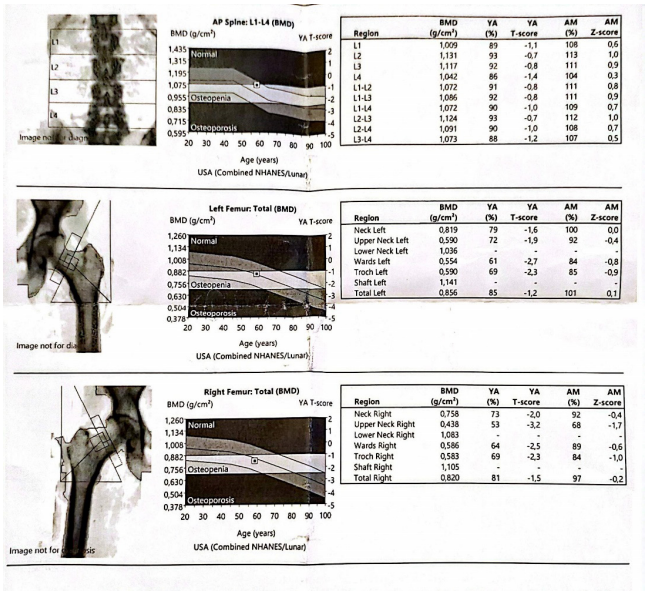
Thyroid ultrasonography: revealed a hypotrophic thyroid gland, with preserved shape, heterogeneous parenchyma, and anechogenic areas consistent with lymphocytic

infiltration, without focal nodular lesions- findings diagnostic of Hashimoto thyroiditis. (fig. 1,2)



(Fig.2)

Dual- energy X-ray absorptiometry (DEXA): demonstrated osteopenia, likely secondary to low BMI and chronic metabolic imbalance (fig.3).



(Fig.3)

Suspicion of LADA

- Based on the following clinical and biochemical features:
- Low BMI and progressive weight loss
- Profound and persistent hyperglycemia
- Marked endogenous insulin deficiency
- Coexisting autoimmune thyroid disease
- Inadequate response to oral antidiabetic therapy

A strong suspicion for Latent Autoimmune Diabetes in Adults (LADA) was raised.

Autoimmune Evaluation

Outpatient testing for type 1 diabetes mellitus- associated autoantibodies yielded the following results (table 4).

Table 4. Autoantibodies

Parameter	Result	Reference Range
Anti- GAD65 antibodies	1288 IU/mL	Neg.<17 IU/mL Poz. >=17 IU/mL
Islet cell antibodies (ICA)	52.40 IU/mL	Neg. <28 IU/mL Poz . >=28 IU/mL
Insulin autoantibodies (IAA)	7.04 IU/mL	Neg. <20 IU/mL Poz. . >=20 IU/mL
IA-2 antibodies	4.99 IU/mL	Neg. <28 IU/ml Poz. >=28 IU/ml

The high-titer positivity of multiple autoantibodies confirmed the diagnosis of LADA.

Follow-Up at 3 Months

At three- month follow-up, the patient demonstrated substantial improvement in metabolic control, with fasting blood glucose of 8.5mmol/L and HbA1c reduced to 7.96%. The patient also presented self-monitored glycemic profiles (table 5), which were reviewed during the consultation and revealed recurrent hypoglycemic episodes occurring predominantly in the evening. Consequently, insulin doses were appropriately reduced: Ins. Lantus 24 IU s.c at bedtime, Ins. Apidra 8+10+10 IU s.c before meals.

Thyroid function normalized (TSH-2.2mIU.L, fT4-20) under adjusted levothyroxine therapy (Euthyrox 125mcg once daily).

Table 5. Five-Day Glycemic Profile (mmol/L)

	Fasting	Pre-lunch	2h Post-lunchh	Pre-dinner	2h Post-dinner
Day 1	8.6	9.8	11.2	4.1	6.8
Day 2	8.3	9.1	10.9	3.8	7.4
Day 3	8	10.2	10.7	4.3	7.6
Day 4	8.1	9.4	11.4	8	6.9
Day 5	7	10	9.5	6.7	6.5

DISCUSSION

The prevalence of T2DM is almost 90–95% in patients with diabetes, while the prevalence of LADA can be 10% in patients with a phenotypic of T2DM, thus indicating a much larger representation than in patients with T1DM.9 Diagnosis of LADA consists of testing for autoantibodies, usually positive for at least one of the four antibodies commonly seen in T1DM. Anti-GAD might not be detectable in early stages but can present over a period of time; hence undetectable anti-GAD level alone cannot rule out LADA. A family history of diabetes is usually present. Management of LADA includes diet, lifestyle, and insulin. Obese LADA (double diabetes) patients may require an individualized regimen of calorie-restricted diet and physical activity. It is also recommended to avoid insulin secretagogues such as glipizide. This is because the stimulation of insulin by these drugs promotes increased autoantigen expression, which accentuates the ongoing autoimmune process.11 Metformin can be used in obese LADA patients, but insulin remains the treatment of choice. Clinicians should also be aware that all diabetic patients including those with LADA have a similar risk of developing cardiovascular and cerebrovascular diseases.12 In addition, LADA patients have a higher risk than T2DM patients for certain autoimmune conditions such as thyroid disease.13

This case illustrates several key features of LADA:

Adult-onset diabetes initially misdiagnosed as Type 2. LADA frequently presents in adulthood and may mimic Type 2 diabetes.

Poor response to oral hypoglycemic therapy. Despite treatment, patients often exhibit suboptimal glycemic control.

Presence of pancreatic autoantibodies. The markedly elevated GAD antibody titer strongly supports an autoimmune etiology.

Gradual progression toward insulin dependence. Insulin therapy becomes necessary as endogenous beta-cell function declines.

CONCLUSION

Definitive guidelines in the management of LADA are not yet available, but early diagnosis of LADA helps patients achieve better glycemic control and avoid the long-term complications of diabetes. Timely adoption of insulin therapy also appears to benefit these patients.

This case illustrates a patient initially misclassified as having type 2 diabetes mellitus, who subsequently demonstrated a progressive autoimmune-mediated ρ-cell failure, culminating in overt insulin dependence. The presence of low BMI, severe insulin deficiency, high titers of pancreatic autoantibodies, poor response to oral antidiabetic agents, and concomitant autoimmune disease unequivocally supports the diagnosis of Latent Autoimmune Diabetes in Adults (LADA).

The case underscores the critical importance of maintaining a high index of clinical suspicion for LADA, particularly in lean adults with rapidly progressive hyperglycemia, early insulin requirement, and coexisting autoimmune disorders, to ensure timely diagnosis and appropriate therapeutic intervention.

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Case report

A DIAGNOSTIC CHALLENGE IN SOFT TISSUE INFECTION: SUPRACLAVICULAR MRSA ABSCESS MIMICKING MUSCULOSKELETAL PATHOLOGY

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ABSTRACT

Introduction: Skin and soft tissue infections (SSTIs) are common clinical conditions, but their presentation may become diagnostically challenging when infection occurs in an anatomically unusual region. Differentiation between non-purulent cellulitis and a localized purulent collection is particularly important because their principal therapeutic approaches differ. Supraclavicular infection may mimic musculoskeletal or vascular disease and may therefore delay definitive treatment.

Case Presentation: A 52-year-old woman presented with progressive erythema, swelling, pain, local warmth, and restricted movement of the right shoulder. Initial orthopedic assessment suggested tendosynovitis. Laboratory evaluation showed leukocytosis and elevated CRP, ESR, and D-dimer, and upper-extremity deep vein thrombosis was considered in the differential diagnosis. Aspiration of the affected area yielded purulent material, with culture demonstrating methicillin-resistant Staphylococcus aureus (MRSA). Empirical clindamycin was initiated and subsequently adjusted to vancomycin plus clindamycin according to the antibiogram. Despite antimicrobial therapy, persistent induration and lack of significant clinical improvement prompted surgical consultation. Surgical exploration confirmed a supraclavicular abscess, and incision, evacuation, lavage, and drainage were performed. The postoperative course was favorable, with rapid clinical improvement and progressive normalization of inflammatory markers.

Conclusion: This case highlights the importance of repeated clinical reassessment in atypical SSTIs. A purulent collection should be distinguished from uncomplicated cellulitis because source control by drainage is central to abscess management. In supraclavicular presentations with shoulder dysfunction, clinicians should maintain a broad differential diagnosis that includes musculoskeletal, vascular, and infectious pathology.

Keywords: MRSA; skin and soft tissue infection; supraclavicular abscess; cellulitis; musculoskeletal mimic; surgical drainage

INTRODUCTION

Skin and soft tissue infections comprise a broad spectrum of disorders involving the skin and subcutaneous tissues and, in more extensive disease, fascia or muscle. They range from uncomplicated superficial infections to deep and potentially life-threatening infections. Their clinical burden is substantial, and early recognition of the extent and nature of infection is essential for appropriate treatment.[1,4]

Cellulitis is a diffuse infection of the dermis and subcutaneous tissue, typically characterized by erythema, warmth, swelling, tenderness, and poorly demarcated inflammatory borders. β-hemolytic streptococci and Staphylococcus aureus are among the principal bacterial

pathogens implicated in SSTIs.[2] In contrast, an abscess represents a localized collection of purulent material. This distinction is clinically important because antimicrobial therapy is the principal treatment for uncomplicated non-purulent cellulitis, whereas drainage is the key intervention when a drainable purulent collection has formed.[1]

The epidemiology of SSTIs has also been influenced by the emergence and spread of community-associated MRSA. S. aureus is a major cause of skin and soft tissue infection, and MRSA may be associated with abscess formation and more complicated clinical presentations. [3] Consequently, microbiological confirmation and susceptibility testing are particularly useful when purulent material is obtained.

Although the extremities are common sites of cellulitis and abscesses, infection in the supraclavicular region is less frequently encountered and may initially resemble pathology of the shoulder girdle, tendons, muscles, lymph nodes, or regional vessels. This overlap can lead to diagnostic delay. The present case describes a supraclavicular MRSA abscess initially interpreted as a musculoskeletal condition, with elevated D-dimer additionally raising concern for upper-extremity thrombosis.

CASE PRESENTATION

A 52-year-old woman presented with progressive erythema, swelling, pain, and restricted movement of the right shoulder over several days. She had previously been evaluated for suspected tendosynovitis.

Physical examination revealed erythema and induration involving the supraclavicular and shoulder region, with significant tenderness and functional limitation of the right upper limb.

Laboratory investigations demonstrated leukocytosis and elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and D-dimer. Because of the elevated D-dimer and symptoms involving the upper limb, upper-extremity deep vein thrombosis was included in the differential diagnosis.

Aspiration of the affected area yielded purulent material. Microbiological culture identified MRSA.

Empirical therapy with clindamycin was initiated and subsequently adjusted to vancomycin plus clindamycin according to the antibiogram. Anticoagulation prophylaxis with enoxaparin was administered.

Despite antimicrobial therapy, persistent induration and insufficient clinical improvement prompted surgical consultation. The patient was transferred to the surgical ward with the diagnosis: “Abscessus regio supraclavicularis et oedema regio omaris et tricipitis brachii lateralis dextrae.”

Surgical treatment consisted of incision, evacuation of purulent material, lavage, and drain placement. Following the procedure, the patient demonstrated rapid symptomatic improvement, with progressive normalization of inflammatory markers. Functional recovery was gradual and complete.

DISCUSSION

The principal diagnostic challenge in this case was the anatomical location of the infection and its clinical overlap with musculoskeletal and vascular disorders. Shoulder pain with restricted movement may lead clinicians toward diagnoses such as tendosynovitis or other periarticular pathology, while swelling of the upper limb accompanied by an elevated D-dimer may raise concern for venous thrombosis. In this setting, the presence of erythema, warmth, induration, and progressive local inflammatory findings should prompt careful consideration of an SSTI.

An important distinction is that cellulitis and abscess are not interchangeable clinical entities. Cellulitis is a diffuse infection without a localized collection of pus, whereas an abscess is a purulent collection requiring source control. Current infectious-disease guidance recommends incision and drainage as the primary treatment for cutaneous abscesses and emphasizes that antimicrobial therapy does not substitute for adequate drainage when a drainable collection is present.[1] The present case illustrates this principle: despite antimicrobial therapy directed against the isolated MRSA, the patient continued to demonstrate persistent induration and inadequate clinical improvement until surgical exploration and drainage were performed.

The microbiological finding of MRSA is clinically relevant. S. aureus is a major pathogen in skin and soft tissue infections, and the increasing importance of community-associated MRSA has altered the microbiological profile and therapeutic considerations of these infections.[3] In purulent infections, obtaining a specimen for culture and susceptibility testing can guide antimicrobial selection,

particularly when initial treatment is unsuccessful or the infection is clinically significant.[1,3]

The elevated D-dimer in this patient contributed to the consideration of upper-extremity deep vein thrombosis. However, D-dimer is a marker of activation of coagulation and fibrinolysis and is not specific for venous thromboembolism. Significant infection and systemic inflammation can also be associated with coagulation activation. Therefore, an elevated D-dimer should be interpreted within the complete clinical context and should not divert attention from local infectious findings. In the present case, the combination of local erythema, induration, purulent aspirate, and positive MRSA culture provided direct evidence of a soft tissue infection.

The supraclavicular location deserves particular attention. Infection in this region may have consequences beyond a superficial local process because of its anatomical relationship with the deep spaces of the neck and upper thorax. The clinical objective is therefore not only to identify the causative organism but also to determine whether the infection has developed into an organized collection requiring surgical source control. Consensus recommendations for SSTIs emphasize prompt recognition, appropriate antimicrobial treatment, and timely drainage or debridement when indicated.[4]

Another important lesson is the value of dynamic reassessment. The initial clinical impression of tendosynovitis was reasonable given the shoulder dysfunction, but the subsequent evolution of erythema, induration, inflammatory markers, purulent aspiration, and microbiological confirmation required diagnostic re-evaluation. Failure to improve despite appropriate antimicrobial therapy should prompt reassessment of the diagnosis, the extent of infection, the presence of a drainable collection, and the adequacy of source control. [1,4]

The case also illustrates the value of multidisciplinary collaboration. Orthopedic, medical/infectious-disease, radiological, and surgical perspectives may be required when infection presents with prominent musculoskeletal or vascular features. Early recognition of an abscess and timely surgical drainage can prevent progression to deeper infection and other complications.

The main limitation of this case report is that the available case documentation contains qualitative laboratory descriptions rather than the exact numerical values of leukocytes, CRP, ESR, and D-dimer. No additional imaging findings should be inferred beyond those documented in the case. Nevertheless, the clinical course, purulent aspiration, MRSA culture, failure of antimicrobial therapy alone, and favorable response after surgical drainage provide a coherent clinical sequence supporting the diagnosis and the main learning points.

CONCLUSION

Supraclavicular SSTI may present with clinical features that mimic musculoskeletal or vascular pathology. In a patient with erythema, swelling, tenderness, restricted shoulder movement, and inflammatory laboratory abnormalities, an infectious cause should remain in the differential diagnosis even when the initial presentation suggests tendosynovitis or thrombosis. Differentiation between cellulitis and an organized abscess is essential because a purulent collection requires effective source control. This case emphasizes the importance of microbiological confirmation, continuous clinical reassessment, multidisciplinary collaboration, and timely surgical drainage when an abscess is identified.

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THE IMPORTANCE OF PHYSICAL THERAPY AND KINESITHERAPY IN THE INJURED IN THE FIRE IN KOCANI – A CASE REPORT

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ABSTRACT

Objective: To present the effect of physical rehabilitation in a patient with burns of the upper limb.

Methods: Case report of a 30-year-old patient with surgically treated burns of IIA–IIB degree of the left hand and forearm, suffered in a fire in Kocani. Physical rehabilitation was carried out with kinesitherapy, manual massage, occupational therapy and ultrasound therapy. The assessment of the functional status was performed by measuring the mobility of the joints and the DASH index at several time intervals.

Results: A gradual improvement in the mobility of the wrist and fingers was noted. The DASH index decreased from 55 points two months after the injury to 5 points after 12 months, indicating significant functional recovery.

Conclusion: Early, continuous and individualized rehabilitation significantly contributes to better functional outcomes, prevention of contractures and improvement of quality of life in burn patients.

Keywords: burns, physical therapy, kinesitherapy

INTRODUCTION

Burns are a type of injury to the skin or other organic tissues that is primarily caused by exposure to heat or other agents such as electricity, radiation, chemicals, etc., but most of them are the result of contact with hot liquids, solids, and flames. According to the World Health Organization (WHO, 2023), burns represent a global public health problem accounting for an estimated 180,000 deaths annually, with non-fatal burn injuries remaining a leading cause of long-term morbidity and functional impairment [10]

Burns are often underestimated as a type of trauma, which besides skin damage, cause complex disorders of other tissues, organs and organ systems. In the case of a burn injury, an assessment is performed with the most important goal of determining its severity, and the four-degree classification allows for a differentiated approach to treatment and interventions. Rehabilitation begins from the moment of injury and continues until the return to everyday activities and is necessary for all patients with superficial or deep burns. Failure to provide adequate rehabilitation results in functional deficits such as reduced mobility, difficulty or inability to perform activities of daily living and return to the work environment.

Rehabilitation procedures include edema reduction, breathing exercises, patient positioning, range-of-motion exercises, and muscle strengthening exercises, which require a multidisciplinary approach and collaboration between the patient, physiotherapist, physicians, nurses, occupational therapists, dietitians, psychologists, and

plastic surgeons.

Recently, the importance of physical rehabilitation is additionaly confirmed through the analysis of cases from the mass accident at the Pulse disco in Kocani, where people suffered burns of varying degrees.

Objective: to demonstrate the effect of physical rehabilitation, including kinesitherapy, manual massage and ultrasound therapy, on improving the mobility and functionality of the upper limb in a patient with surgically treated burns of IIA–IIB degree.

Case report: Patient A.M., aged 30, was admitted to the Department of Plastic and Reconstructive Surgery on 16.03.2025 after burns sustained in a fire in a disco in Kocani. Upon admission, a burn of the right upper arm, left hand and dorsum was diagnosed, with an extension of 15% TBSA and a depth of IIa/b degree. Surgical treatment with debridement and local wound treatment was performed, but due to the severity of the injuries she was referred to Zagreb. After completing hospital treatment in Zagreb, she was again registered at the Plastic Surgery Department with a diagnosis of post-combustio of the head, chest, right upper arm, left forearm and hand, with an assessment of the remaining surface area of approximately 10% TBSA, with IIA–IIB degree. The advanced phase of healing was recorded, with a granulating base and superficial epithelialization.

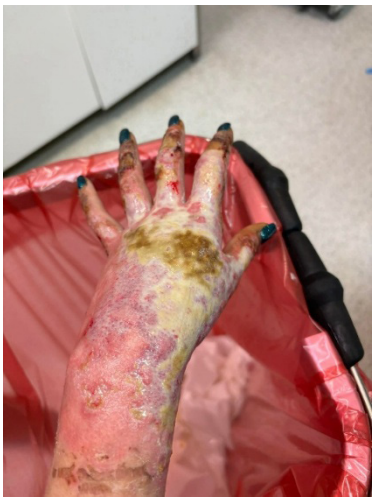


Figure 1. Thermal burns on the left hand on admission

With a stabilized local and general status and without active complications, the patient was discharged from Plastic Surgery and began a rehabilitation process at the Department of Physical Medicine in the PHI OB with extended activity - Kocani, where she was treated several times for 21 days. Measurements of the mobility of the injured left arm were made (Table 1, Table 2 and Table 3) and a DASH index was performed, at the first examination (2 months after the injury), at 4 months after the injury, and 11 months after the injury (Table 4). At the first examination, the local finding showed the presence of scars in the neck area, both shoulders, right upper arm and left wrist and hand. Wrist movements were severely limited in palmar flexion, with slight limitation in dorsiflexion, and various limitations were registered in the fingers: in the base joint, impossible movements, PIP of the first finger with limited flexion, the second finger limited or impossible, and the remaining fingers moved within a normal range. Opposition of the thumb was possible to normal, while abduction was limited. Kinesitherapy was started, which includes active, corrective and actively assisted exercises, occupational therapy and manual massage.

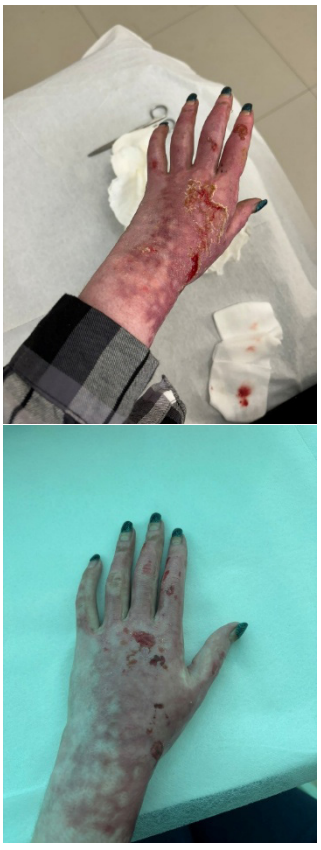


Figure 2. Left hand 4 months after thermal injury

During follow-up examinations, the local finding gradually improved in terms of movements in the wrist and fingers, with extension from possible to normal, except in the PIP of the second finger, while the remaining fingers showed a gradual increase in flexibility, so that in the following period the movements in the wrist became almost normal, with additional progress in the flexibility of the fingers and thumb. With continued treatment 11 months after the injury, the patient showed almost normal movements in all joints

Figure 3. Left hand 11 months after injury

Table 1. Table 1. Mobility of the left hand wrist during physical treatment

	Wrist	
	Flexion	Extension
First examination (2 months after injury)	85	50
4 months after injury	N	60
11 months after injury	N	N

Table 2. Flexion of left gand fingers during physical treatment

Left hand - FLEXION	Finger I		Finger II			Finger III			Finger IV			Finger V		
	MCF	DIP	MCF	DIP	PIP	MCF	DIP	PIP	MCF	DIP	PIP	MCF	DIP	PIP
2m after injury	30		34	95	51	60	95	65	60	100	45	40	100	80
4m after injury	35	50	60	70	20	60	65	40	60	65	40	55	45	50
11m after injury	55	80	80	95	60	80	95	75	80	95	70	65	95	70

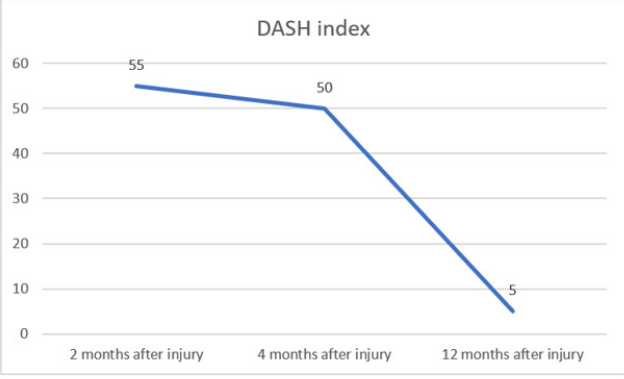
Table 3. Extension of left hand fingers during physical treatment

Left hand - EXTENSION	Finger I		Finger II			Finger III			Finger IV			Finger V		
	MCF	DIP	MCF	DIP	PIP	MCF	DIP	PIP	MCF	DIP	PIP	MCF	DIP	PIP
2m after injury	N	N	30	-45	N	N	N	N	N	N	N	N	N	N
4m after injury	N	N	N	N	N	N	N	N	N	N	N	N	N	N
11m after injury	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Table 4. DASH index during physical treatment

Left hand	DASH index
2 months after injury	55
4 months after injury	50
12 months after injury	5

Chart 1. DASH index during physical treatment



Conclusion: Early, continuous and individually tailored physical rehabilitation is an important and necessary part of the treatment of burn patients, especially when the upper extremities are affected and there is a risk of developing contractures, limited mobility and functional deficit. The application of physical therapy contributes to improving the range of motion, reducing scarring and improving the functional ability and quality of life of patients.

The presented case confirms that a multidisciplinary approach and regular rehabilitation treatment enable significant functional recovery and an easier return to daily activities. The obtained results demonstrate the importance for clearly defined and clinically applicable rehabilitation protocols in burn patients, in order to achieve optimal functional outcomes and prevent long-term complications.

Discussion: The therapeutic protocol initiated at the PHI OB Kocani–comprising active-assisted and corrective exercises, manual scar massage, occupational therapy, and ultrasound therapy–directly contributed to reversing initial severe ROM restrictions. At the initial evaluation (2 months post-injury), the patient exhibited severe limitation in wrist palmar flexion (85°) and dorsiflexion (50°), alongside complete immobility in the metacarpophalangeal (MCP) joints of the second digit and constrained proximal interphalangeal (PIP) joint flexion. This clinical presentation aligns with findings by Dunpath et al. (2016), who reported that post-burn immobilization primarily impairs complex multi-joint hand mechanics.

By implementing structured kinesitherapy and manual massage, mechanical stress was systematically applied to the remodeling connective tissue. As demonstrated in the literature by Procter (2010) and Edgar (2009), early dynamic mobilization prevents pathologically rigid collagen cross-linking during scar maturation. Over the 11-month rehabilitation period, patient A.M. achieved near-normal range of motion across all wrist and digital segments, with full recovery of wrist flexion/extension and resolution of digital extension deficits (from -45° at 2 months to normal at 11 months).

Quantitative functional assessment using the DASH (Disabilities of the Arm, Shoulder and Hand) outcome measure further confirms the success of this comprehensive approach. The patient's DASH score declined dramatically from 55 points (indicating severe upper extremity disability) at 2 months post-injury to 50 points at 4 months, ultimately reaching 5 points at 12 months, which represents near-complete restoration of functional independence in activities of daily living. These numerical gains mirror the outcomes described by Gomez et al. (2017) and Rrecaj et al. (2015), who highlighted that continuous, long-term physical rehabilitation is directly correlated with significant improvements in upper extremity functional indexes and overall patient quality of life.

Furthermore, the multidisciplinary approach–combining acute surgical management (debridement and graft site care) with tailored outpatient physical therapy–was essential in managing both the primary skin injury and secondary musculoskeletal sequelae. As noted by Jeschke et al. (2020) and Mudawarima et al. (2017), holistic rehabilitation strategies that combine joint mobilization, scar management, and functional retraining are mandatory to achieve complete physical and psychological recovery in severe burn survivors.

In summary, the substantial functional recovery demonstrated in this case report highlights that early, individualized, and sustained physical rehabilitation is vital to preventing contractures, restoring joint range of motion, and ensuring complete functional reintegration following deep dermal hand burns.

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Profesional paper

MANAGEMENT OF TWO IVF PREGNANCIES IN A PATIENT WITH A BICORNUATE UTERUS WITH ONE CERVIX AND A TOTAL OCCLUSION OF BOTH TUBES

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ABSTRACT

Introduction: Congenital malformations of the female reproductive organs can occur in the vagina, cervix, uterus, and fallopian tubes. They are most common in the uterus, and bicornuate uterus is a malformation caused by abnormal Mullerian fusion. Very often this result in recurrent miscarriages, fetal growth retardation, premature births, and malpresentations in pregnancy.

Case report: Two pregnancies achieved with IVF will be presented, in a patient with a bicornuate uterus with a single cervix and total occlusion of both tubes. The patient came in hospital at the age of 26 and had never conceived before. As a young girl at age of 15, she was operated from hematometra as a result of inperforated hymen and at the same time there was an unsuccessful attempt to perform a Strassmann operation- a classic but complicated operation to join the two horns of the uterus, as an idea for a possible future successful pregnancy.

After several investigations and medical interventions from our side, the patient achieved two successful pregnancies with IVF, which ended as premature births at 32 and 34 weeks of gestation, with a interval between the two pregnancies of six years. Both pregnancies were without major complications, but due to the smaller capacity of the left horn of the uterus, both ended with premature birth and cesarean section.

Conclusion: Today there are many ways with assisted fertilization and careful management of pregnancy, to realize conception and pregnancy in women with congenital genital anomalies.

Key words: bicornuate uterus, mullerian anomaly, pregnancy, preterm delivery, single cervix.

INTRODUCTION

Congenital malformations of the female reproductive organs can occur in the vagina, cervix, uterus and fallopian tubes [1]. Congenital uterine malformations are present in about 5% of women and are the cause of 10% of recurrent miscarriages and about 25% of late miscarriages and premature births [2]. They are most common in the uterus and bicornuate uterus is a malformation caused by abnormal partial failure in fusion of the Mullerian ducts, resulting in a uterus divided into two horns, that is often accompanied by obstetric complications during the pregnancy and occurs with a prevalence of 0.4% [3]. The bicornuate uterus is classified as a class IV Müllerian duct anomaly and has two subtypes in relation to the cervix. A bicornuate uterus with one cervical canal in which central myometrium extends to the internal cervical os and a bicornuate uterus with two cervical canals where central myometrium extends to the external cervical os [2] [3]. The septum that forms between the two horns of the uterus sometimes extends to the vagina and completely divides the uterus and vagina into two parts in 25% of cases. Often these anomalies are accompanied

by anomalies of the kidneys and renal ducts [4].

Achieving pregnancy in congenital anomalies of the uterus and cervix is always more difficult than achieving conception in normal uterus and cervix [4]. They are often associated with infertility, repeated miscarriages, abnormal presentation of the fetus during pregnancy and most often cesarean delivery, premature births, low birth weight and IUGR- intrauterine growth retardation, or inadequate contractions, increased perinatal mortality [5]. Uterine anomalies are most often detected with imaging techniques such as 3D ultrasound, HSG or MRI and with surgical techniques such as hysteroscopy and laparoscopy [6] [7]. This paper show that pregnancy is possible even with uterine anomalies and reduced capacity of the uterine cavity, only if the entire situation is managed well and if the patient has faith that it can happen.

CASE PRESENTATION

A case of two pregnancies achieved with IVF will be presented, in a patient with a bicornuate uterus and single cervix, divided into two horns to the internal cervical os, which completely separates the uterus into two horns without communication between them. The cervix which began with a single cervical canal then divided higher into two canals towards the two horns of the uterus. The patient came to us at the age of 26, after being told in Kosovo that all attempts to get pregnant would be unsuccessful, due to a uterine anomaly, a smaller capacity of uterine horns, and blocked tubes.

The patient had never conceived before and was 26 years old, with a regular menstrual bleedings. As a 15-year-old girl, she underwent emergency surgery for an inperforated hymen and hematometra, during which and infraumbilical incision was made in order to attempt a Strassmann operation, but it was not performed and only the problem with the imperforate hymen was resolved. Since then, she has started menstruating regularly and and she had no further investigations until she got married.

During the first ultrasound examination with 3D ultrasound, we diagnosed that it was a bicornuate uterus, divided up to the cervix. The uterine horns were widely divergent, with big angle between them to the top and symmetric uterine horns, with an anteroposterior diameter of 30 mm and with an equally swollen endometrium. Ovaries with normal placement, morphology and size were detected and sausage-shaped uterine tubes filled with fluid, during the same ultrasound examination. In a vaginal examination with speculum, it was seen that there was no vaginal septum and that only one cervix was involved. Further diagnostic procedures with hysterosalpingography-HSG and then hysteroscopy-HSC and laparoscopy-LPSC procedures were indicated, to assess the capacity of the uterus horns and for possible correction, as well as definitive determination of the fluidity of both tubes.

Diagnostic procedures before pregnancy:

- After the first menstrual cycle, an HSG was performed and the injected contrast showed that there was a single cervix that branches at the top into two channels that lead to both uterine horns. The left horn was clearly shown to be filling with contrast, while the right horn showed a filling defect. Both tubes were shown to be hydrosalpingitic without free outflow of contrast into the abdominal cavity (figure 1).

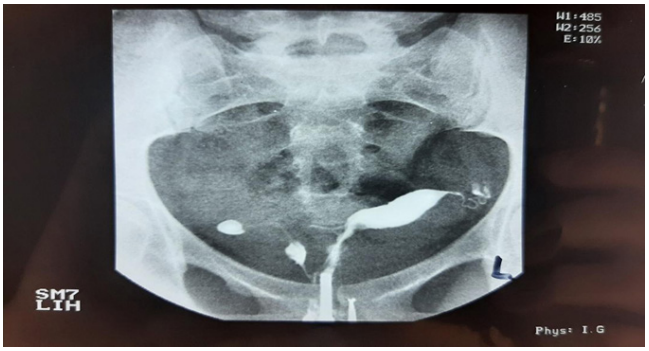

Figure 1. HSG in bicornuate uterus with single cervix and total occlusion of both tubes

It was decided not to do an MRI, but to go for a laparoscopy and hysteroscopy, to assess the capacity of both uterine horns, for possible correction and management of the hydrosalpingitic tubes.

- Laparoscopy and hysteroscopic surgical interventions were performed and there was one cervical canal continues to the left and right horns of the uterus, in the upper part of the cervix. The hysteroscopic evaluation showed a free uterine left horn with good capacity. During the hysteroscopic evaluation of the right uterine horn, it was seen that it had a smaller capacity and adhesions in the uterine cavity, especially in the upper part of the right horn.

With laparoscopy, a camera was inserted into the abdomen and the uterus was shown with concave or heart-shaped external uterine contour, and the uterine

horns were widely divergent. The fundal cleft was deep and descended to the lower third between the two horns. The ovaries were shown with normal position, morphology and size. Due to the visible bilateral hydrosalpinx, hydrosalpingitics tubes were removed and there was no any operative corrections of both uterine horns. With that, the patient was ready and prepared for IVF, as the only chance to get pregnant.

Stimulation protocol and IVF procedure:

A stimulation protocol was started and after the stimulation was performed, a follicle puncture was scheduled, during which 6 good oocytes were obtained, 4 of which were fertilized and one blastocyst was returned to the left uterine horn, which was with better capacity and without adhesions.

Two weeks after the embryo transfer - ET in the left horn, a pregnancy test was done which was positive and ultrasound showed a gestational sac (figure 2). At the next examination in the fifth week of gestation, an ultrasound detected a yolk sac and an embryo.

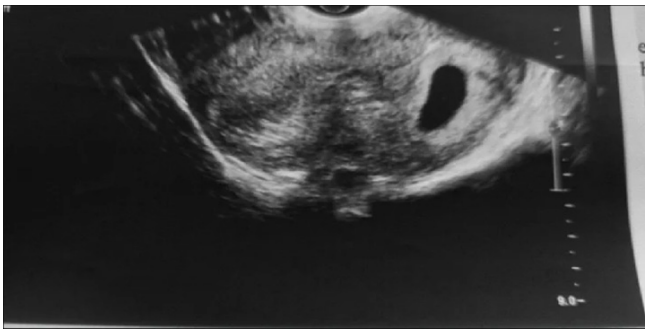

Figure 2. Gestational sac in the left horn of bicornuate uterus

Vitamin therapy with folates, gestagens locally and bed rest were prescribed to the start of the pregnancy. The pregnancy was monitored as all pregnancies, with all screenings recommended for normal pregnancy and regular measurement of the length of the cervix.

During each ultrasound examination, the growth and development of the fetus and the length of the cervix were monitored, the placenta was on the anterior wall of the left horn, placed high above the isthmic part in the same uterine horn. The fetus developed and grew normally for the gestational age, during all examinations and the patient had no uterine activity utill 29 gestational week of pregnancy, due to the lower capacity of the uterine cavum in the uterine horn.

The first uterine activity appeared in 29 week and tocolysis and fetal maturation with corticosteroids were indicated and given. Uterine activity calmed down, with continued therapy with gestagens, magnesium and bed rest. After two weeks contractions were repeated and intensified. Contractions this time caused rupture of the amniotic fluid at 31.5 weeks of gestation and again tocolysis and maturation with corticosteroids for the fetal lungs were indicated, as more than two weeks had passed since the previous maturation with corticosteroids. The repeated contractions did not stop and since there was no progress in the cervical findings, it was decided to complete the delivery by cesarean section at 32.4 weeks of gestation.

The cesarean section was performed with dorsoposterior presentation of the fetus and live female fetus was born with weight 1620 grams and 43 cm. length, with Apgar-score AS 8/9. No communication with the right uterine horn was found during the cesarian section. The patient was treated postoperatively with antibiotic, uterotonic and antithrombotic therapy and left the hospital on the 4-th day after the cesarean section.

The newborn was kept in the neonatal intensive care unit-NICU, without respiratory support and was released 18 days after birth with a weight of 2120 grams and a length of 45 cm. Due to the timely maturation and the maximum delay of delivery until the full 32nd week of gestation, due to the smaller capacity in the uterine horn, there were no complications for the mother and fetus, caused by pregnancy and delivery.

Six years later, when the patient was 33 years old, she decided to have a second pregnancy. The same procedure with stimulation and IVF and one embryo was returned again in the left uterine horn as before.

The entire pregnancy was without complications and the first uterine activity appeared later this time, at 32 gestational week and were managed with tocolysis. They recurred at 34 weeks of gestation and tocolysis and corticosteroid maturation of the fetal lungs were administered. One day after completion of corticosteroid maturation, due to intense uterine contractions, the patient delivered by cesarean section at 34.3 weeks. The pregnancy ended with a Caesarean section and a live female fetus weighing 1820 grams and a length of 45 cm. with Apgar- score AS 8/9 was born. Again there were no complications for the fetus and the mother. The mother left the hospital 4 days after the surgery, and the newborn, who was without respiratory support, weighing

2200 grams, was discharged from the neonatal intensive care unit ten days after delivery in good condition.

With this, the patient became a mother twice, with good management of conception, pregnancy and childbirth.

DISCUSSION

This case describes a clinically interesting and rare case of high- risk uterine anomaly and two successful IVF pregnancies in a patient with bicornuate uterus and bilateral tubal occlusion. With detailed reproductive and obstetrics management, both pregnancies were achieved with IVF, were managed similarly and ended with cesarean deliveries, with the delivery of live and healthy neonates.

Pregnancy in women with uterine anomalies is possible and if the anomaly is not detected before pregnancy, very often result in recurrent miscarriages, fetal growth retardation, premature births, and malpresentations [4]. These pregnancies are less successful than pregnancies carried in a normal uterus [5]. Imaging techniques are very important in detecting anomalies of the female genital tract and as a result of their use some of the anomalies can be diagnosed and successfully corrected [6] [7]. Some of them are uncorrectable but still, all options should be tried in such cases to get pregnant [8].

Most uterine anomalies are detected with 3D ultrasound,than hysterosalpingography, MRI, hysteroscopy, and laparoscopy [6] [8].

By ASRM classification this is a bicornuate uterus in class IV a, malformation caused by abnormal partial failure in fusion of the Mullerian ducts, resulting in a uterus divided into two horns, which should be differentiated from septate uterus and uterus didelphys [9]. Surgical intervention is usually not indicated in this case, unlike a septated uterus where hysteroscopic resection of the septum is usually recommended [10].

A bicornuate uterus increases the risk for miscarriage, preterm delivery, fetal malpresentations which increase the risk for cesarean section delivery and cervical insufficiency. Despite these elevated risks, many women still achieve successful, viable full-term deliveries [4].

Pregnancy with bicornuate uterus with single cervix can cause various perinatal outcomes including miscarriage (21%), prematurity (24%), ectopic pregnancy (2%), IUGR (11%) and increased incidence of caesarean section (84%) [11].

The use of progestogens and bed rest has been shown not to increase the success rate of these pregnancies [12].

Patients should not be discouraged when such anomalies are discovered, but rather should be encouraged to use all save medical options to become pregnant. All possible ways to achieve this goal should be used.

Although we were not completely confident from the first moment that everything would end in success, we took the risk and step by step, together with the patient, we reached the ultimate goal, achieving two pregnancies and giving birth of two premature but healthy newborns.

Both pregnancies were achieved with IVF, were managed similarly and ended with cesarean deliveries in 32 and 34 weeks of pregnancy.

CONCLUSION

A bicornuate uterus with a single cervix is one of the rare uterine anomalies. Early diagnosis and preparation of these patients for pregnancy and good antenatal care lead to success in pregnancy and childbirth. There are no strict clinical protocols for managing such pregnancies and each case is individual and different in the management of pregnancy. The method of delivery in these pregnancies is different, but most often due to the smaller capacity of the uterine horns and malpresentations, the births end with a cesarean section.

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LOOKING BEYOND THE CORONARY LESION: INDIVIDUALIZED DEVICE SELECTION USING DRUG-COATED BALLOON ANGIOPLASTY GUIDED BY BLEEDING RISK ASSESSMENT–A CASE REPORT

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ABSTRACT

Background: Drug-coated balloon (DCB) angioplasty is an established treatment option for selected de novo coronary lesions, particularly in small-vessel disease. In patients at high bleeding risk (HBR), individualized revascularization strategies based on bleeding risk assessment may енабле abbreviated dual antiplatelet therapy (DAPT) and simplify the management of subsequent bleeding events.

Case Summary: A 59-year-old woman with hypertension, hyperlipidemia, active smoking, recurrent nephrolithiasis, previous spontaneous hematuria, and iron-deficiency anemia presented with non-ST-elevation myocardial infarction (NSTEMI). Bleeding risk assessment according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria identified two major HBR criteria. Coronary angiography demonstrated a 95–99% subtotal stenosis of the distal right coronary artery. Following successful lesion preparation, percutaneous coronary intervention was performed using a 2.75 × 20 mm paclitaxel-coated DCB without stent implantation. One month later, the patient developed recurrent gross hematuria with a hemoglobin decrease from 109 to 97 g/L, requiring urological intervention. After completion of one month of DAPT, antiplatelet therapy was de-escalated without recurrent ischemic events. At six-month follow-up, the patient remained asymptomatic, with no evidence of myocardial ischemia and complete recovery following laser lithotripsy.

Discussion: This case demonstrates that DCB-only angioplasty may represent a valuable revascularization strategy in carefully selected HBR patients with suitable coronary anatomy. Systematic bleeding risk assessment before PCI can guide device selection, allow flexible DAPT duration, and facilitate management of subsequent non-cardiac interventions without compromising short-term clinical outcomes.

INTRODUCTION

Percutaneous coronary intervention (PCI) with drug-eluting stent implantation remains the standard treatment for most patients undergoing coronary revascularization. Nevertheless, treatment of small coronary vessels continues to represent a challenge because of higher rates of restenosis and the need for prolonged dual antiplatelet therapy following metallic stent implantation. Drug-coated balloons have emerged as an effective “leave-nothing-behind” strategy by delivering an antiproliferative drug without permanent scaffold implantation. During the past decade, several

randomized studies have demonstrated non-inferiority of DCB compared with contemporary DES in selected de novo small-vessel lesions. (1,2,3,4)

The evolution of percutaneous coronary intervention (PCI) over the years has facilitated treatment of increasingly complex patient populations like patients at high bleeding risk (HBR). The challenges in defining the optimal management of patients undergoing PCI at HBR include a shortage of relevant clinical data and the use of heterogeneous definitions of HBR that limit interpretation and generalization in this group of patients. (5) So, besides anatomical considerations, in this group of patients, increasing attention has been directed toward individualized PCI planning according to bleeding risk. Patients with previous bleeding episodes, chronic anemia, or anticipated need for surgical intervention represent a subgroup in whom abbreviated DAPT may become particularly important. (6)

Contemporary PCI planning extends beyond coronary anatomy alone. Current ESC guidelines yecommend routine bleeding risk assessment before coronary intervention to guide antithrombotic treatment and optimize patient outcomes. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) (5) criteria have become the reference standard for identifying patients at increased bleeding risk undergoing PCI, while the PRECISE-DAPT (7) score may further assist in determining the appropriate duration of dual antiplatelet therapy. Although these tools provide objective risk stratification, they should complement rather than replace individualized clinical decision making, particularly when additional patient-specific factors suggest a high probability of future bleeding or the need for non-cardiac surgical intervention.

We present a patient with NSTEMI successfully treated with DCB angioplasty in whom the anticipated bleeding risk became clinically relevant only one month after PCI, confirming the rationale behind the initial treatment strategy.

CASE PRESENTATION

A 59-year-old woman with a history of hypertension, hyperlipidemia, active smoking, and a positive family history of premature coronary artery disease was admitted with a chest pain of two days. The patient's medical history included recurrent nephrolithiasis complicated by episodes of hematuria and iron-deficiency anemia, with last hospitalization and implantation of double-J catheter 5 months earlier and recommendation for laser lithotripsy by the attending urologist, which was not performed until the admission.

The electrocardiogram showed no significant ischemic changes, while high-sensitivity cardiac troponin I was markedly elevated (890 ng/L), consistent with a diagnosis of non-ST-elevation myocardial infarction (NSTEMI). The admission hemoglobin was 109 g/L (10.9 g/dL), reflecting mild anemia. Transthoracic echocardiography revealed mildly reduced left ventricular systolic function (left ventricular ejection fraction [LVEF] 50%) with newly developed inferior wall hypokinesia and no significant structural abnormalities (LVEDD 52 mm, LVESD 23 mm, LA 38 mm, IVSd 10 mm).

High bleeding risk assesment

Due to the history of anemia and according to the 2023 ESC Guidelines for Acute Coronary Syndromes (8), bleeding risk was assessed before coronary intervention according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria (5) (Figure 1). The patient fulfilled two major criteria – spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or any time, if recurrent and Hemoglobin <11 g/dL which classified this patient at high bleeding risk.

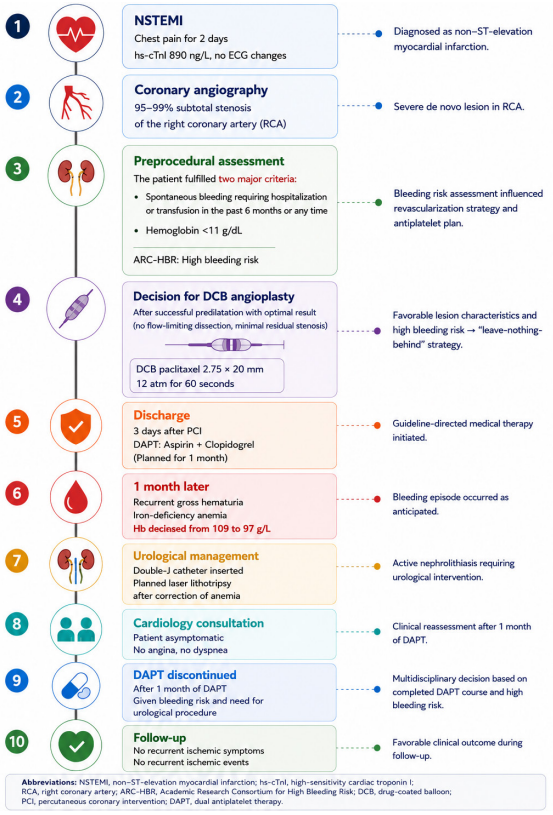
Major HBR criteria	Minor HBR criteria
• Anticipated long-term oral anticoagulation	• Age ≥75 y
• Severe/End-stage CKD (eGFR <30ml/min)	• Moderate CKD (eGFR 30-59 ml/min)
• Hb <11g/dl	• Hb 11 – 12.9 g/dl for men and 11 – 11.9 g/dl for women
• Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or any time, if recurrent	• Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
• Moderate/severe baseline thrombocytopenia (<100x10^9/L)	• Long-term use of oral NSAIDs or steroids
• Chronic bleeding diathesis	• Any ischemic stroke at any time not meeting the major criterion
• Liver cirrhosis with portal hypertension	
• Active malignancy (excluding nonmelanoma skin cancer) within the past 12 months)	According to ARC HBR definition - patients are considered to be at HBR if at least **1 major and 2 minor criteria** are met
• Previous spontaneous ICH (at any time)/ traumatic ICH (within the past 12 months)/ presence of a bAVM/ moderate or severe ischemic stroke within the past 6 mo	
• Nondeferrable major surgery on DAPT	
• Recent major surgery or major trauma within 30 d before PCI	

Figure 1. Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria (5)

Coronary angiography demonstrated a 95–99% subtotal stenosis of the distal segment of the right coronary artery. Following successful lesion preparation with balloon predilatation and an optimal angiographic result without flow-limiting dissection or significant residual stenosis, the lesion was considered suitable for a drug-coated balloon (DCB)-only strategy. Considering both the favourable lesion characteristics and the patient's increased bleeding risk with a foreseeable need for future urological intervention, PCI was completed using a 2.75

× 20 mm paclitaxel-coated balloon inflated at 12 atm for 60 seconds, without stent implantation. An excellent immediate angiographic result was achieved, with restoration of TIMI 3 flow. The postprocedural period was uneventful, and the patient was discharged after three days on dual antiplatelet therapy with aspirin and clopidogrel.

At the follow-up at one month after PCI, the patient reported one week of recurrent haematuria, laboratory evaluation demonstrated low hemoglobin concentration of 97 g/L (9.7 g/dL). Urological assessment confirmed active nephrolithiasis, with recommendation for cardiology consultation for therapy modification and laser lithotripsy recommended following correction of the anemia. The patient reported no angina symptoms and denied dyspnea or exercise intolerance. Given the planned risk of bleeding events, followed by DCB angioplasty, we discontinued the P2Y12 inhibitor and lowered the dose of aspirin to 75mg. Previously planned urological intervention was performed two weeks after without ischemic events or symptoms reported. During the 6 months follow-up, the patient remained free of angina, and exercise stress testing showed no evidence of myocardial ischemia, with complete recovery from the urology intervention and normal hemoglobin of 134 g/L (13.4 g/dL). (Figure 2)



DISCUSSION

Contemporary PCI planning extends beyond achieving an optimal angiographic result. Current ESC guidelines recommend routine assessment of both ischemic and bleeding risk before coronary intervention to personalized revascularization and antithrombotic treatment.(9, 10) The ARC-HBR criteria have become the standard tool for identifying patients at increased risk of major bleeding after PCI (5). In our patient, although the need for urological intervention was not immediate, the combination of recurrent hematuria, chronic anemia, and untreated nephrolithiasis suggested a high likelihood of future bleeding events, supporting the selection of a strategy that would permit shorter DAPT if necessary.

Patients at high bleeding risk (HBR) represent an increasingly common population undergoing PCI, prompting a paradigm shift towards individualized antithrombotic strategies that balance protection from ischemic events against the risk of major bleeding. Several randomized trials have demonstrated that shortening DAPT in carefully selected HBR patients reduces bleeding without a significant increase in major adverse cardiovascular events. In the MASTER DAPT trial (11), discontinuation of DAPT after one month in ARC-HBR patients who had undergone implantation of a biodegradable-polymer sirolimus-eluting stent was non-inferior to standard-duration therapy with respect to net adverse clinical events and major adverse cardiac or cerebral events, while significantly reducing major or clinically relevant non-major bleeding. Similarly, the XIENCE 28 and XIENCE 90 (12) studies demonstrated that one month of DAPT followed by single antiplatelet therapy in HBR patients treated with contemporary drug-eluting stents resulted in low rates of ischemic events and significantly less bleeding compared with longer DAPT regimens. These findings have been reinforced by subsequent meta-analyses showing that abbreviated DAPT, particularly when limited to one to three months, is associated with a substantial reduction in bleeding without compromising cardiovascular outcomes in appropriately selected HBR patients (13).

These data have been incorporated into contemporary ESC guidelines, which recommend routine bleeding risk assessment before PCI using validated tools such as the ARC-HBR criteria and acknowledge abbreviated DAPT as an appropriate strategy in patients in whom bleeding risk outweighs ischemic risk. While most evidence supporting short DAPT originates from studies

of contemporary drug-eluting stents, the rationale for abbreviated antiplatelet therapy may be even stronger after drug-coated balloon (DCB)-only angioplasty, where no permanent intracoronary scaffold remains and the risk of stent thrombosis is eliminated. Consequently, DCB has emerged as an attractive revascularization strategy for selected HBR patients, particularly when we anticipated the need for early interruption of antiplatelet therapy due to bleeding or non-cardiac surgery. Elimination of the permanent implant may reduce chronic vascular inflammation, facilitate restoration of normal vasomotor function, and eliminate late complications related to metallic stents, including late stent thrombosis and neoatherosclerosis, with consequently a greater flexibility regarding the duration of DAPT. (Table 1)

Consideration	DES	DCB	Relevance in this patient
Permanent metallic implant	Yes	No	Favoured DCB
Small-vessel disease	Acceptable	Evidence-supported	Favoured DCB
Expected DAPT duration	Generally longer in many ACS settings (12 months)	May be abbreviated in selected patients (4 weeks	Favoured DCB
Future urological intervention	Potentially complicates antiplatelet management	Greater flexibility	Favoured DCB
History of bleeding	Requires careful DAPT planning	Supports individualized DCB strategy	Favoured DCB

Table 1. Clinical Rationale for Drug-Eluting Balloon Selection Over Drug-Eluting Stent Implantation

Several randomized clinical trials and subsequent meta-analyses have demonstrated that DCB angioplasty is non-inferior to contemporary DES for selected de novo small-vessel coronary lesions. Studies including BASKET-SMALL 2 (1), RESTORE SVD China (3), PICCOLETO II, (2) and other contemporary trials have shown comparable rates of target lesion failure, myocardial infarction, and cardiac death, while maintaining acceptable rates of target lesion revascularization and confirmed the use of DCB as an established treatment option, particularly when adequate lesion preparation can be achieved and significant residual stenosis or flow-limiting dissection are absent.

This case also highlights the importance of multidisciplinary management. Close collaboration between interventional cardiologists and urologists allowed appropriate balancing of bleeding and thrombotic risks while avoiding unnecessary delays in definitive treatment of the underlying urological disease. Such collaboration is particularly relevant in HBR patients, in whom competing clinical priorities frequently require individualized treatment decisions beyond standard guideline recommendations.

The results of this case supports the concept that bleeding risk assessment should influence PCI strategy before rather than after coronary intervention. In this particular patient if treatment option was use of DES, the management of following recurrent hematuria would have been considerably more challenging because interruption of DAPT during the early post-PCI period with a greater risk of stent thrombosis. In contrast, the DCB-only strategy provided sufficient flexibility to shorten antiplatelet therapy when clinically required, while maintaining an excellent clinical outcome.

CONCLUSION

This case demonstrates that a DCB-only PCI strategy may represent a valuable revascularization option in carefully selected HBR patients with suitable coronary anatomy. Systematic bleeding risk assessment before PCI, combined with precise lesion preparation and appropriate patient selection, may allow successful coronary revascularization while preserving flexibility for abbreviated antiplatelet therapy and future non-cardiac interventions. As evidence supporting DCB use continues to expand, this approach may become increasingly relevant in the growing population of patients in whom bleeding risk is a major determinant of therapeutic decision-making.

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Case report

МУЛТИПЛИ БАЗОЦЕЛУЛАРНИ КАРЦИНОМИ НА ЛИЦЕТО: ПРЕДИЗВИЦИ ВО ХИРУРШКАТА ЕКСЦИЗИЈА И РЕКОНСТРУКЦИЈА – ПРИКАЗ НА СЛУЧАЈ

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АПСТРАКТ

Базоцелуларниот карцином (BCC) е најчестиот малиген тумор на кожата (80% застапеност,кога станува збор за немеланомските кожни карциноми). Иако се карактеризира со спор раст и низок метастатски потенцијал, одредени хистолошки подтипови, особено инфилтративните форми, покажуваат агресивно локално однесување, повисок ризик за рецидив и претставуваат значаен предизвик во хируршкиот третман.

Приказ на случај: Презентираме случај на инфилтративен базоцелуларен карцином локализиран во централната лицева регија, кој ги зафаќа дорзумот на носот, медијалниот кантуси базоцелуларен карцином на аурикулата. Туморот беше третиран со двофазен хируршки пристап со цел постигнување на комплетна ексцизија со хистолошки чисти маргини. Поради обемноста на дефектот, реконструкцијата беше реализирана со комбинирана примена на Paramedian forehead флап, Mustardé флап, Buccal advancement флап и Antia–Buch флап за реконструкција на аурикулата.

Резултати: Комбинираниот хируршки и реконструктивен пристап овозможи комплетно отстранување на туморот со хистолошки чисти маргини, без рани постоперативни компликации. Постигнат беше задоволителен функционален и естетски исход, со зачувување на контурите и симетријата на лицето.

Клучни зборови: базоцелуларен карцином (BCC); Paramedian forehead флап; Mustardé флап; Antia–Buch флап

ВОВЕД

Најчести малигни неоплазми на кожата се базоцелуларниот карцином, планоцелуларниот карцином и малигниот меланом (1–3). Базоцелуларниот карцином е споро растечки тумор кој ретко метастазира (4,5), за разлика од планоцелуларниот карцином и малигниот меланом, кои имаат поагресивен тек, потенцијал за метастазирање во регионалните лимфни јазли, а меланомот и во далечни органи (мозок, коски и бубрези) (6–9).

Природниот процес на стареење и прекумерната изложеност на сончева светлина се тесно поврзани со појавата на кожни лезии, кои се почести кај постарата популација (10). Дополнително, хроничната иритација на кожата и траумaтизацијата на невуси претставуваат значајни ризик-фактори. Во последно време, зголемената изложеност на ултравиолетово (УВ) зрачење, како природно така и вештачко, особено кај помладата популација, го зголемува ризикот за развој на кожни карциноми во поодминатa возраст (11–13).

Базоцелуларниот карцином (BCC) е најчестиот тип на кожен карцином и сочинува околу 80% од немеланомските карциноми на кожа. Најчесто се јавува на лицето, особено на анатомски проминентните региони изложени на УВ зрачење. Хируршкиот третман претставува предизвик поради неговата локализација (14).

Средната лицева регија (нос, медијален кантус и

усни) има највисока инциденца на кожни карциноми (15). Инвазивните форми можат да инфилтрираат во подлабоките структури, вклучувајќи мускул, рскавица и коска (16,17).

Ексцизијата на кожни карциноми често е ограничена поради недостаток на ткиво за реконструкција, што може да доведе до несоодветни хируршки маргини и последователен рецидив (18). Поради тоа, постигнувањето на хистолошки чисти маргини е од суштинско значење, бидејќи присуството на туморски клетки значително го зголемува ризикот од повторна појава на карциномот (19).

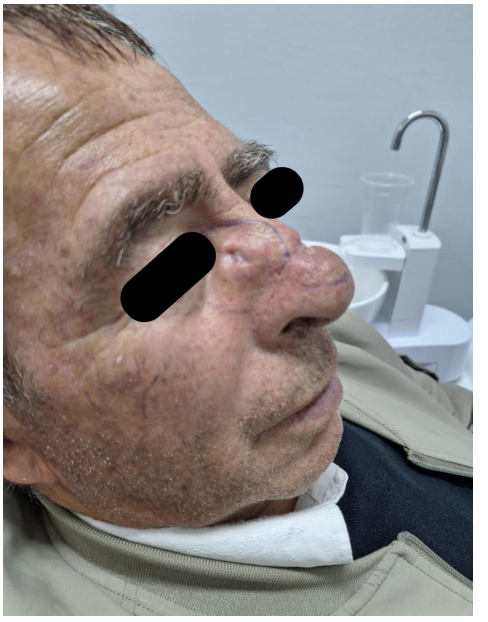
Во главно се користат три методи за обезбедување на адекватни хируршки маргини: микрографска Mohs хирургија, frozen section хистолошка анализа и стеџ хирургија со перманентна патологија. Иако Mohs хирургијата обезбедува најдобри резултати, не е секогаш достапна поради потребата од високо специјализиран кадар. Frozen section методата овозможува интраоперативна проценка, но е поврзана со релативно висок процент на позитивни или блиски маргини (11–15%) (20–22). Стеџ хирургијата со перманентна патологија овозможува прецизна анализа и можност за дополнителна ексцизија пред конечната реконструкција.

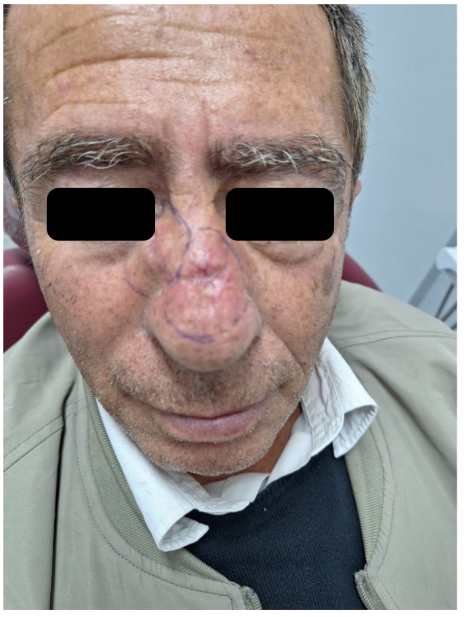
Иако базоцелуларниот карцином генерално има низок метастатски потенцијал, одредени хистолошки подтипови, како микронодуларниот и инфилтративниот, покажуваат поагресивно локално однесување и поголем ризик за рецидив. Современите дијагностички методи, како дермоскопија и оптичка кохерентна томографија, овозможуваат порано откривање и попрецизно планирање на третманот (23).

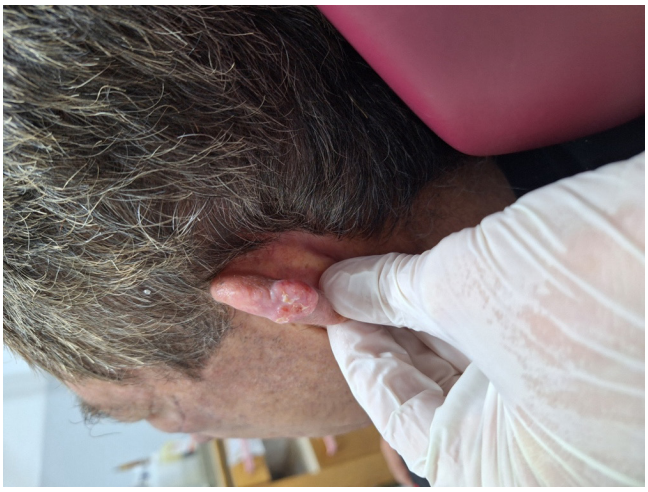
Третманот на базоцелуларниот карцином се состои во хируршка ексцизија со хистолошки чисти маргини, со цел минимизирање на ризикот од рецидив (24). Препорачаните хируршки маргини изнесуваат 4–5 mm за нискоризични тумори и околу 6 mm за агресивни форми (25).

ПРИКАЗ НА СЛУЧАЈ

64 годишен пациент доаѓа на нашата Клиника со базоцелуларен карцином на носот,односно два базоцелуларни карциноми на кожата на носот, со димензии од 2 cm, од кои едниот непосредно под десниот медијален кантус и десната страна на носот, а другиот на дорзумот на носот, непосредно над апексот на носот, како и базоцелуларен карцином на левата аурикула. Анамнестички, дава податок за ексцизија на базоцелуларниот карцином, на десната страна на носот во друга институција, пред 2 години, но не приложува писмен документ за истата, ниту пак патохистолошки наод. Со оглед на тоа дека анатомијата на лицето веќе беше видно изменета, пациентот се согласи на хируршки зафат. Во втората фаза на зафатот, беше ексцидиран е базоцелуларен карцином на левата аурикула и дефектот беше реконструиран со Antia Buch flap.



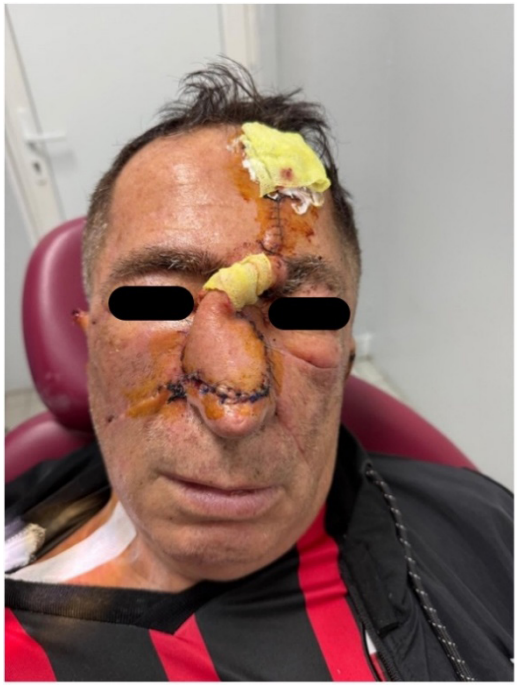




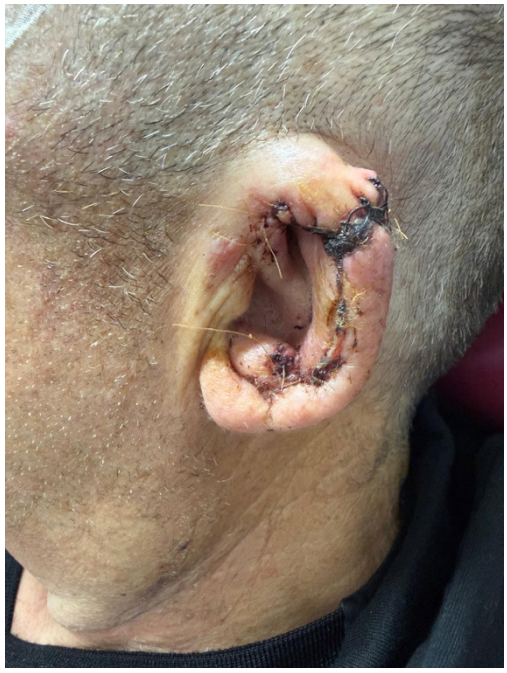
Состојба на пациентот пред операција

Хируршка техника

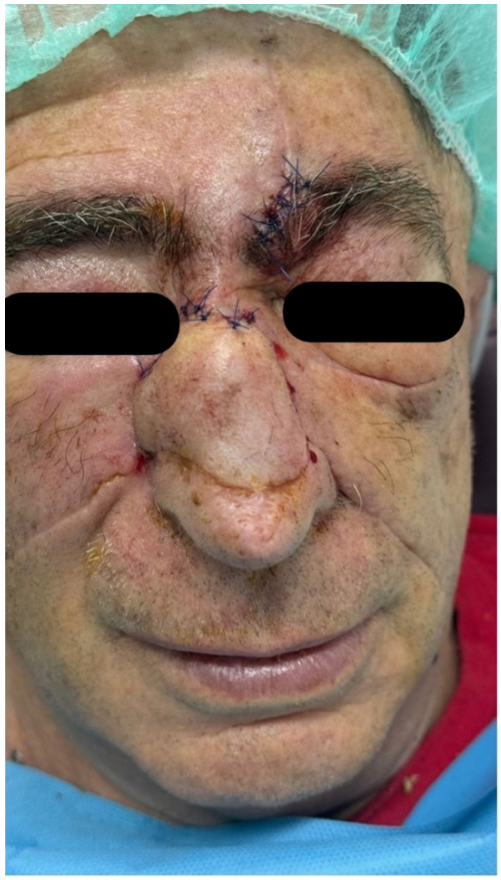
Дефектите на дорзумот на носот, латералната страна на носот, односно десниот мезијален кантус, беа реконструирани со: Paramedian forehead flap, Buccal advancemet flap и Mustardé flap последователно. Дефектот на левата аурикула е реконструиран со Antia buch flap.



Трет ден пост оперативно



Трет ден пост оперативно



Три недели пост оперативно

Три месеци пост оперативно

ДИСКУСИЈА

Овој приказ на случај ја отсликува комплексноста во менаџирањето на инфилтративниот базоцелуларен карцином на кожата на лицето, кој често бара третман во два или повеќе стадиуми.

Bichakjian et al. (26) и Cameron et al. (27) истакнуваат дека високоризичниот базоцелуларен карцином со инвазивни карактеристики има зголемена склоност кон рецидив и бара агресивен хируршки пристап, комбиниран со напредни реконструктивни техники. Кај рекурентните случаи, најдобри резултати се постигнуваат со мултимодален пристап, кој може да вклучува и системска терапија како хемотерапија или имунотерапија (28). Ова ја нагласува важноста на мултидисциплинарен пристап во кој учествуваат дерматолози, онколози и хирурзи.

Во реконструкцијата на назални дефекти, парамедијалниот челен флап (Paramedian forehead flap) претставува златен стандард (29). Овој флап обезбедува сигурна васкуларизација и добар естетски и функционален резултат. Стапката на неуспех е релативно ниска, околу 6%, а најчеста причина е нарушената васкуларизација, особено при компромитирана венска дренажа, што може да доведе до конгестија и некроза на флапот (30,31). Кај реконструкција на апексот на носот се препорачува соодветно истенчување на флапот и користење на ‹рскавичен графт за подобра потпора.

Дополнително, примената на принципот на анатомски поединици овозможува оптимален естетски резултат, со поставување на лузните во природните контури и намалување на ризикот од контрактури и дехисценција (32).

Mustardé флапот, првично опишан за реконструкција на долниот очен капак, денес се користи за реконструкција на дефекти на лицето со полна дебелина (33). Неговите предности се добрата васкуларизација, соодветната боја и текстура, како и редукцијата на ткивната тензија, со што се намалува ризикот од ектропија (34). Со соодветни модификации, може успешно да се примени и кај дефекти на латералниот ѕид на носот.

Во прикажаниот случај, со Mustardé флап беше постигнато успешно затворање на дефектот во регијата на медијалниот десен кантус и десната страна на носот, додека дефектот на дорзумот на носот беше реконструиран со парамедијален челен флап во две фази. Поради обемноста на дефектот и потребата за ексцизија во здраво ткиво, беше применет и Buccal advancement флап на контралатералната страна на лицето.

Реконструкцијата на аурикулата претставува дополнителен хируршки предизвик поради присуството на ‘рскавица и тенка кожа, што ја зголемува склоноста кон деформации и некроза. Малите дефекти (<1–1.5 cm) може да се затворат со примарна ексцизија, додека поголемите бараат реконструкција со флап или графт (35). Во овој случај, дефектот на левата аурикула (2cm) беше успешно реконструиран со Antia–Buch флап, со одличен постоперативен резултат.

Обемната реконструкција резултираше со значително подобрување на контурите на лицето, со ефект сличен на facelift. Финалниот естетски и функционален исход беше одличен, како од перспектива на пациентот, така и за целиот хируршки тим.

ЗАКЛУЧОК

Инфилтративниот базоцелуларен карцином на лицето претставува значаен хируршки и онколошки предизвик, особено кај рекурентните форми и лезиите со висок ризик. Навремената дијагноза и адекватниот хируршки третман со постигнување на хистолошки чисти маргини се клучни за намалување на ризикот од

рецидив.

Парамедијалниот челен флап останува златен стандард за реконструкција на комплексни назални дефекти, додека Mustardé флапот и другите локални флапови овозможуваат сигурно затворање со добар естетски и функционален исход.

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Case report

SHTATZËNIA E NJË PACIENTES ME UREMI E TRAJTUAR ME HEMODIALIZE (HD) KRONIKE

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ABSTRACT

Gratë me insuficience renale kronike terminale (IRKT-uremi) qe trajtohen me hemodialize (HD) konike intermitente kan gjasa minimale të mbeten shtatzëna dhe janë më të ndjeshme ndaj komplikacioneve gravidare krahasuar me grate me funksion normal të veshkave,prandaj shtatzanite pacientet me IRKT konsiderohen shtatzëni me rrezik tejet të lartë, si për nënës ashtu edhe të fetusit dhe për këtë arsye menaxhimi i tyre kërkon nje angazhim tepërbashkëta të nefrologëve, gjinekologëve-obstetrikrik,nonatologeve, infermierëve dhe nutricionistëve. Shtatzënia në pacientet me IRKT dhe në trajtim me HD jane tepeEr te rralla dhe sfiduese. Menaxhimi i ketyre shtatzanive konsiston në: rritja e frekuences dhe kohës në dializë, perdorimi i mbranave biokompatibili High Flux sipas mundesive te mbershtjellura me tokoferol, ajtja e niveleve të ulëta të uresë para dializës, kontrollimin e presionit te gjakut,anemise ekuilibrimin e elektrolitetve,respektim dietetikc dhe mirembjtje te pesehs se thate trupore, kujdes ndaj infeksioneve te fistules arterio-venoze apo traktit urinar, monitorimi adekuat i fetusit etj. Frekuenca e shtatzënisë tek gratë në dializë është jashtëzakonisht e ulët, po me kalimin e viteve, ka pasur një rritje të incidencës së shtatzënive tek pacientët me HD dhe një përmirësim në rezultatet e nënës dhe të fetusit [1,2].Qellimi i punimit: Raportohet një rast i një gruaje me IRKT (stadin e V), në trajtim me hemodializë për 2 vjet, që mbeti shtatzënë dhe solli një foshnje të shëndetshme me peshë 2.5 kg përmes sectio caesarea. Në këtë punim, ne propozojmë një rishikim të literaturës aktuale rreth kësaj teme, duke paraqitur edhe përvojën tonë.Ne punim I kemi përfshir edhe analizat labotratorike dhënat laboratorike para dhe pas dializës,menaxhimin e anemisë me ESA dhe strategjitë multidisciplinare që ndikojne ne mirembajtjen e shtatzanise.

HYRJE

Shtatzënia tek gratë me sëmundje kronike të veshkave gjithmone është konsideruar si një ngjarje sfiduese si për nënën,për fetusin por edhe per nefrologet. Me permiresimin e modaliteteve te trajtimit me HD kalimin e viteve, janë arritur disa përmirësime në rezultatin e pacientëve shtatzëna me IRKT te trajtura me rritje të shkallës së lindjeve të suksesshme.Nje numer i studimeve mbi kete dukuri sugjerojen se mundësia e suksesit të shtatzënisë varet nga strategjitë e menaxhimit adekuate te seancave te HD,llojit te membranes, tretjes dialitke, kohezgjatjes se séances si dhe intenzifilimi i seancave te HD.Per her te pare ne vitin 1971 nga Confortini et al. u pershkrua shtazania e sukseshme e nje pacientes me ERSD e trajtura me hemodialize[3,4].

Prej kohesh rezultatet e shtatzënisë tek pacientët me IRKT te trajturaa me HD janë konsideruar jashtëzakonisht si te pafavorshme , dhe literatura në lidhje me shtatzëninë gjatë dializës deri më sot ofron vetëm disa studime ose seri rastesh. Sipas njohurive tona, nuk ekzistojne studime apo prova klinike dhe rekomandime apo udhezime te publikuar mbi kete dukuri. Shoqata Italiane e Nefrologeve

sebashku meshoqatene e Gjinekologjisë dhe Obstetrikës kan dhene disa rekomandime të bazuara në ekpseriencen e tyre mbi menaxhimin edhe komplikmet e shtazanise te grate me IRKT te trajtuara me HD.[5,6,7]. Sëmundja kronike renale (SKR) prek afërsisht 3% të grave në moshë riprodhuese dhe është një faktor për shtatzëni me rrezik të lartë. Me uljen Në shkallën e filtrimit glomerular , ka një ulje progresive të pjellorisë dhe një rritje të rrezikut të rezultateve të pafavorshme të shtatzënisë. Ne literature bashkekohore ka pak punime mbi shtazanine te pacietet me ESRD si dhe mbi menaxhimin e tyre [8,9] Hiperprolaktinemia dhe nivelet e ulëta të estradiolit në serum të vërejtura në pacientët me dializë janë të lidhura me ndryshimet në hormonin çlirues të gonadotropinës dhe boshtin hipotalamik-hipofizar-gonadal, dhe mund të shpjegojnë vështirësitë në ovulim. Shtatzënia në grate me ESRD është e lidhur me rrezik të lartë për komplikacione obstetrike dhe fetale. Megjithatë, intensifikimi i dializës dhe monitorimi frekuent i laboratorëve rrit mundësinë për lindje të suksesshme [10,11]. Fatmiresisht përqindja e shtatzënive të suksesshme viteve te fundit është rritur vazhdimisht(me permiresimine e modaliteteve,membranat me tokoferol,kohezgjatja e dializes,intenzifikimi javor I dijalizes) , por ende ekziston një shkallë shumë e lartë e vdekshmërisë dhe morbiditetit të nënës/fetusit krahasura me popullatën normale. Për të arritur një lindje të suksesshme, kjo situatë kërkon angazhiom te veqante te nefrologëve, gjinekologëve, dhe nutricionistëve. Edhe pse nuk kemi fakte të dokumentuara mirë, besohet se frekuenca e shtatzënive te gratë në HD është në rritje, nga 1% në 7%, sipas botimeve më të fundit, me norma të ndryshme në vende të ndryshme.[12,13,14].

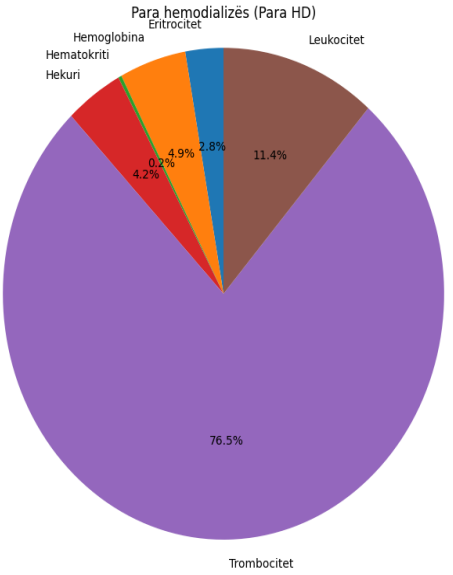
Qellimi i punimit: Raportohet një rast i një gruaje me IRKT (stadin e V), në trajtim me hemodializë për 2 vjet, që mbeti shtatzënë dhe solli një foshnje të shëndetshme me peshë 2.5 kg përmes sectio caesarea. Në këtë punim, ne propozojmë një rishikim të literaturës aktuale rreth kësaj teme, duke paraqitur edhe përvojën tonë.Ne punim I kemi përfshir edhe analizat labotratorike dhënat laboratorike para dhe pas dializës,menaxhimin e anemisë me ESA dhe strategjitë multidisciplinare që ndikojne ne mirembajtjen e shtatzanise.

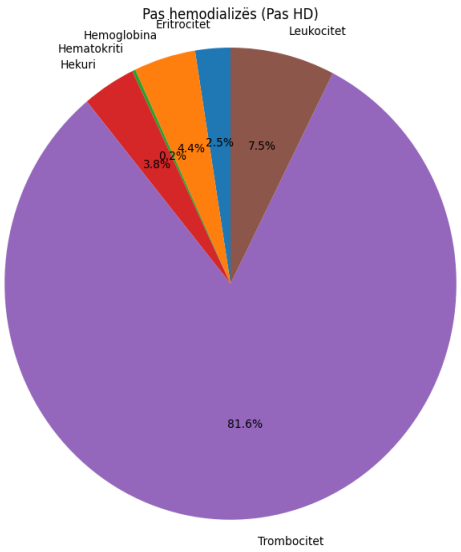
Prezantim i rastit: Gruaja, 28 vjeçare me uremi e trajtur me HD bikrbonate me membrane biokompatbile High Flux mbi mbi 26 muaj ne Spitalin Klinik te Tetoves,Reprti i Nefrologjise dhe Hemodializes me frekuence prej 3x ne jave nga 4 ore. Me qe pacientja disa jave shfaqte manifestime te shpeshta gastrointestinale-nauze,fryerje te stomakut (dukuri te zakonshme te kjo grupe e pecienteve) na preferuam kontrolle te gjinekologu ku me ane te ultratingullit u verifikua se pacientja eshte shtatzane (jave e 6-7) dhe na u detyruam qe te pergadisim protokol (duke konsultuar edhe literature mbi keto raste) te veqant per menaxhimin e kesaj shtazanie.Filluam me ekzaminmet e paraqitura ne tabelen1,2,3 dhe duke e shpeshtuar frekuencen dhe kohezgjatjen e dializes

Tabela numer 1: Vlerat laboratorike te pasqyres se gjakut para dhe pas Hemodializës(HD)

Parametrat e Hemogramit	Para HD	Pas HD
Eritrocitet 1012 /L(V.R=4.2-5.5	3420 ↓	3.70
Hemoglobina (VR=7.76-10.60 mmol/l	6.00 ↓	6.50
Hematokriti(VR=0.37-0.53)	0.30 ↓	0.34
Hekuri ((VR=7.3-28 µmol/l)	5.20 ↓	5.6
Trombocitet 109/L (VR=140-340)	94 ↓	120
Leukocitet 109 /L(4-9)	14.0↑	11.0 ↑

Nga vete tabela verehet nje anemi, trombocitopeni (ulje e trombociteve) dhe leukociteoze e lehte si pasoje e infeksionit(qe eshte shume e zakont te pacientet me ESRD te trajtur me Hemodialize).

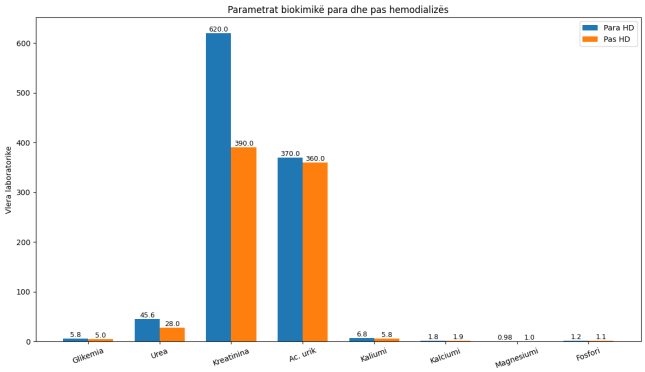




Parametra	Para HD	Pas HD
Glikemia (VR=3.5-6.5 mmol/	5,8	5.0
Urea(s),VR=2.0-6.3 mmol/	45.60	28.0
Kreatinina(s),VR=71-125 µmol/l	620.0	390.0
Ac.urik(s),VR=155-357 µmol/l	370.0	360.0
Kaliumi,VR=3.8-5.6 mmol/l	6.80	5.80
Kalciumi,VR=2.1-2.6 mmol/l	1.80	1.90
Magnesiumi,VR=0.7-1.0 mmol/l	0.98	1.00
Fosfori joorganik,VR=0.8=1.58mmol/l	1.20	1.10

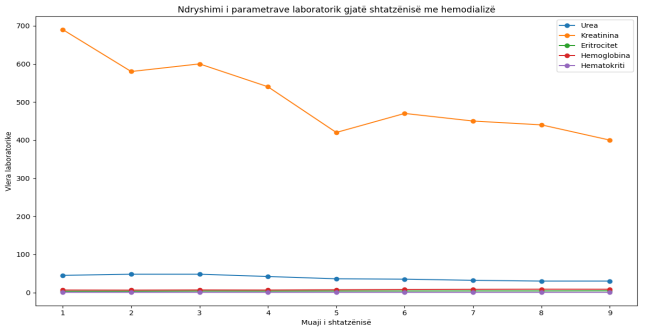
Nga vete tabela numer 2 verehet se vlerat para HD tregojnë per uremi ndërsa pas HD verehet një ulje të nivelit të ures,kreatinines dhe ekuilibrim te lehte te elektrolitteve(K,Ca,Mg dhe fosforit).

Tabela numer 2: Vlerat laboratorike (para dhe pas hemodializes)te:glikemise,Ureseneserum(Us),keratinines ne serum(Crs) acidit urik, kaliumit, kalciumit, fosforit joorganik dhe Magneziumit



Muaji i shtatzanise	Urea	Kreatinin	Er	Hb	Htc	HD ne jave(ore)	ESA +Hekur+Vit.C
1	45.0	690.0	3.40	6.50	0.35	3x4 (12 ore ne jave)	3x2000 IE-Epo +Fe+Vit.C
2	48.0	580.0	3.40	6.30	0.32	3x4 (12 ore ne jave)	3x2000 IE Epo +Fe +Vit.C
3	48.0	600.0	3.80	6.70	0.38	3x4.5 (13.5 ore ne jave	3x2000 IE Epo
4	42.0	540.0	3.70	6.50	0.36	3x4.5 (14 ore ne jave	3x2000 IE Epo+Fe
5	36.0	420.0	3.90	7.20	0.40	3x 5 (15 ore ne jave)	3x2000 IE Epo +Vit.c
6	35.0	470.0	4.00	8.00	0.40	4x4 (16 ore ne jave)	3x2000 IE Epo
7	32.0	4.50.0	4.20	8.40	0.40	5x3.5 (17.5 ore ne jave)	3x2000 IE Epo
8	30.0	440.0	4.20	8.70	0.42	5x4(20 ore ne jave)	3x2000 IE Epo +Fe+Vit.C
9	30.0	400.0	4.50	8.60	0.45	5x4 (20 ore ne jave)	3x2000 IE Epo+Fe+Vit.C

Tabela numer 3: Tregon vlerat laboratorike,frekuencen javore te seancave te HD,trajtimi i anemies ë gjatë shtatzënisë (muaj pas muaji)



Me kalimin e muajeve te graviditetit na filluam ne menyre graduale te intenzifikojme frekuencen dhe oret e trajtimit te HD për të ulur perqendrimet e parametrave degraduese te azotit ndersa aplikimi i terpaise me ESA(Erythropoiesis Stimulating Agens) dhe preprate te hekurit e ndihmuam rritjen e niveleve te Er(Eritrocitev e),Hb(Hemoglobines) dhe Htc(Hematokritit).Pacienten ne javet e fundit e hospitalizuam,konsulltuam gjinekolog edhe neonatologun dhe anesteziologun per planifikim te lindjes me sektio cesarea,ne diten qe nuk ishte ne diajlize dhe pas nje menaxhimi multidisciplinar (me mjeke nefrolog,obstetric,pedijater-neonatolog) , mundesuam nje lindje te sigurt te nje foshnje te gjinise mashkullore prej 2.4 kg pa komplikme neonatale. Gjate seancave te HD si antikogulant na kemi perdor heparinen sepse nuk eshte terratogjen dhe nuk e kalon placneten ndersa kumarina nuk jepete dhe eshte e kunderindikuar.

DISKUTIMI

Nje numer me i madh e pacientëve me IRKT te trajtuara me HD kronike kanë mosfunksionim seksual si rezultat i problemeve fizike dhe/ose emocionale /endokrine. Fertiliteti te keto paciente kryesisht bie mosfunksionimit hipotalamik/hipofizar i cili rezulton me mosfunksionim ovarial dhe cikle te nderprera mandej per shkak të an emisë,hiperprolaktinemisë,humbken e deshires per seks,depresionit etj.[15,16].Mirepo me permiresimin e efikasitetit dhe modaliteteve te dializës(perdorimi i membranave dialitike me tokoferol,HighFlux,intenz ifikimi i frekuences dhe kohezgjatjes se HD(5 here ne jave nga 5x4...5x3,5 ore ne javet)dhe ndikoi dukshem ne uljen e urese,kreatinines ,korrigjimet e anemisë me ESA dukshem ndikojne ne mirembajtjene e shtatzanise duke e rrite perqendrimin e Er.Hb dhe Htc. [17,18]. Hemodializa intensive (>17.5-20 orë/javë) përmirëson ecurine e shtatzanise duke ulur toksinat uremike dhe stabilizuar elektrolitet.Terapia me ESA është e sigurt dhe efektive gjatë shtatzënisë për aneminë në CKD, duke reduktuar nevojën për transfuzione te gjakut.Menaxhimi multidisiplinar është me se I nevojshem për optimizimin e shëndetit të nënës dhe fetusit.Rasti jone tregon se shtatzënia e suksesshme është e mundur edhe në grate me IRKT te trajtura me HD kronike me nje angazhim professional dhe dhe monitorim intensive [19,20].Në vitin 1980, një seri rastesh u botuana në regjistrin e Shoqatës Evropiane të Dializës dhe Transplantit (European Dialysis and Transplant Association-EDTA) që përfshinte 1300 gra në moshë riprodhuese, duke raportuar një shkallë incidence prej 0.9% të shtatzënive te pacientët në HD intermitente kronike. Në vitin 1994, Hou botoi një seri tjetër rastesh nga 206 njësi dialize të Amerikës së Veriut. Përqindja e abortit spontan ishte 70% para vitit 1990 dhe nën 40% në vitet në vijim.Nga viti 2000 filloi te rritete numrii i grave shtatzane me IRKT te trajtura me HD dhe u raportua nje numer i madh i shtatzanive te suksesshme > 70%. [21,22,23,24].Sipas literaturës së disponueshme mbi këtë temë, masat që duhen marrë për të arritur shtatzëni të suksesshme tek këto paciente përfshijnë: qasje multidisiplinare, kohëzgjatje të shtuar në dializë, mbajtjen e niveleve të ulëta të uresë para dializës, parandalimin e lindjes së parakohshme, kontroll të rreptë të presionit të gjakut dhe niveleve të elektroliteve, parandalimin e infeksioneve urinare dhe monitorim adekuat të fetusit.Ushqyerja e paciente shtazane duhet te jete me konzumimin e kalorive me 30-35 kcal/ditë ose konsumimin e 1-1.5 g/kg peshë (hemodializë) proteina shtesë çdo ditë për të siguruar zhvillimin e fetusit,acid folik 1 mg/ditë duke filluar nga tremujori i pare dhe konsumimin e 1500 mg/ditë kalciumdhe konsumimin e vitaminave,Gjate periudhes se shtatzanise grate me dilize shtimin ne peshe duhet ta rregullojne konfrom pershes se fetusit peshen ashtu qe në tremujorin e parë, nëna duhet të shtojë të paktën 1-1.5kg duke u rritur deri ne 0.45 kg. Vëllimii gjakut të nënës dhe shtimi në peshë duhet të jenë ne proporcion me fazën e shtatzënisë.Dozat e ultrafiltrimit duhet të rregullohete individualishte në mënyrë që të evitohet hypovolemia, hipotensioni arterial, hipovolemisë dhe aritmisë. Humbja e tepert e peshës së nënës për shkak të ultrafiltrimit të shpejtë dhe të tepërt mund të zvogëlojë perfuzionin e gjakut fetal-placentar e cila mund të jetë shumë e dëmshme për fetusin.Nivelet e kaliumit në tertejen dialitike dializat duhet të jene prej 3-3.5 mmol/l për të shmangur hipokaleminë, ndersa perqendrimet e Kalciumit ne tretjen dialitike gjate HD ditore përqendrim kalciumi në dializat duhet preferohet te jete 2.5mEq/l.3, ndersa nivelet e bikarbonatit, duhet rregulluar me përqendrime të ulëta prej 25 mEq/l). [25].

Te grate me uremi te trajtuara me HD si komplikime me te shpeshta janë: hipertensioni arterial,abort spontan, shkëputje placen-tare,anemia,infeksionet, këputje të parakohshme të membranave, polihidramnion, lindje të parakohshme, preeklampsia/eklampsia, hemorragji, nevojë për prerje cezariane dhe vdekje të nënës. Komplikacionet më të shepshte të fetusit te grate shtatzane te trajtura me HD janë: lindja e parakohshme, rritja e kufizuar intrauterine,vuajtja akute dhe kronike e fetusit,vështirësia në frymëmarrje tek i porsalinduri, vdekja mitrale ose neonatale. [26]. Afërsisht 80% e grave shtatzane me ESRD dhe HD kanë hipertension arterial ose kërkojnë trajtim medikamnetoz antihipertensiv por trajtimi fillestra konsistom me rregullimin e vëllimit duke përdorur ultrafiltrimin adekuat ,duke patur parasysh qe nxjerrja e lëngjeve gjate HD mos jete e tepert qe mos shfaqe hipoperfuzionin në organe të ndryshme.Pacientja jone ne fillim te trimestrit te trete filloi te shfaqe hypertension prej160/90 mg dhe na filluam trajtimin me Methyldopa (Aldomet) me dozim prej 3x250 mg ne ditet dhe Nifedipine me dozim 2x10 mg/dite.Pasi u konstatua shtazania na filluam te zgjasim edhe kohen e trajtimit me HD ne 6 dite ne javet por me kohzghjatje prej 4.5 oreve pasi pacientja e respektont peshen trupore midis seancave te HD.Çdo muaj (ndonjehre edhe dy here ne muajt) te pacientja kryheshin edhe analizat me protokol nefrologjik dhe hemogrami (Er,Hb,HtcThr,Le)) me qellim qe te ndiqet pasqyra e gjakut dhe nieveli i kreatinines, urese,acidit urik,elektrolitet(Na,K,Ca,fosfori joorganik (inP),hekuri ne serum.Presioni i gjakut ne fillim te HD ishte 180/100 mmHg pas hemodializes ishte 140/90..130/90 mmHG. ACE frenuesit janë të kundërindikuar gjatë shtatzënisë (për shkak të rrezikut të lartë të fetotoksicitetit, duke përfshirë edhe keqformimet kongjenitale).[27].

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Shtatzënia tek gratë me ESRD te trajtura me HD eshte tejet e veshtire per menaxhim dhe perfundim te lindjes se se sukseshme sepse kerkon nje angazhim multidisciplinar. Ne perfundim na mund te konkludojme se edhe grate me ESRD te trajturaa me HD mund të kenë shtatzëni të suksesshme si qe ishte rasti jone.Shpreojme se rasti dhe prvoja jone do te kontribuon në literaturën mbi menaxhimin e suksesshem te shtatzanise te grate me ESRD te trajtuara me HD kronke intermitente.

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case report or brief communication - up to 6 pages and a maximum of 3 tables and / or figures/images.

Leter up to 2 pages

With the manuscript, provide a page giving the title of the paper; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. (see Additional Information for Authors)

Provide an abstract of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five key words or short phrases should be added to the bottom of the abstract page.

Quotations of references in the text should primarily be from journals indexed in PubMed which have proven their significance. The style of references required by Medicus is the Vancouver format (see Additional Information for Authors).

Except for units of measurement, abbreviations are discouraged. The first time an abbreviation appears it should be preceded by the words for which it stands.

The international generic names should be used for all drugs. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

All manuscript sent to the editor should be noted by the authors whether they are meant for the "original research papers" section or the rest of the journal's content.

The authors receive two copies of the relevant issue.

Informacione plotësuese për autorët

I. Faqja e parë – ballina: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

II. Faqja e dytë – abstrakti dhe fjalët kyqe: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

III. Faqja e tretë dhe të tjerat – teksti i plotë i artikullit: Teksti i plotë i artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë (trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

Additional Information for Authors

I. First page - front page: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - abstract and keywords: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – full text of the article: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e dorëshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjëqë do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vrojtimit gjatë realizimit të studimeve të verbuara. Definoni termet statistikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përmbledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e probabilitetit (p) dhe të tregoni se është shprehës (sinjifikant në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

Interval – CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë mendon për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin "Vancouver", referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Një punim mund të ketë më së shumti një autor dhe 4 koautor. Koautori i fundit duhet të jetë mentori ose koautori më i afëërt me punimin. Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text. Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

One article can have one author and 4 co-author. Last co-author is the mentor of the article or closest co-author of the paper." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics. The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. N Engl J Med 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. BMJ 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. National service framework for coronary heart disease. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; Udhërrëfyes i shkurtër i ShoqatësShqiptaretëKardiologjisëpërparandalimineSëmundjes AterosklerotikeKardiovaskularenëpraktikënklinike,Tiranë,2006
7. Azemi M, Shala M, dhe bp. Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papublikuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bërjen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për ilustrimet (figurat): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. N Engl J Med 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. BMJ 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. National service framework for coronary heart disease. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for illustrations (figures): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).