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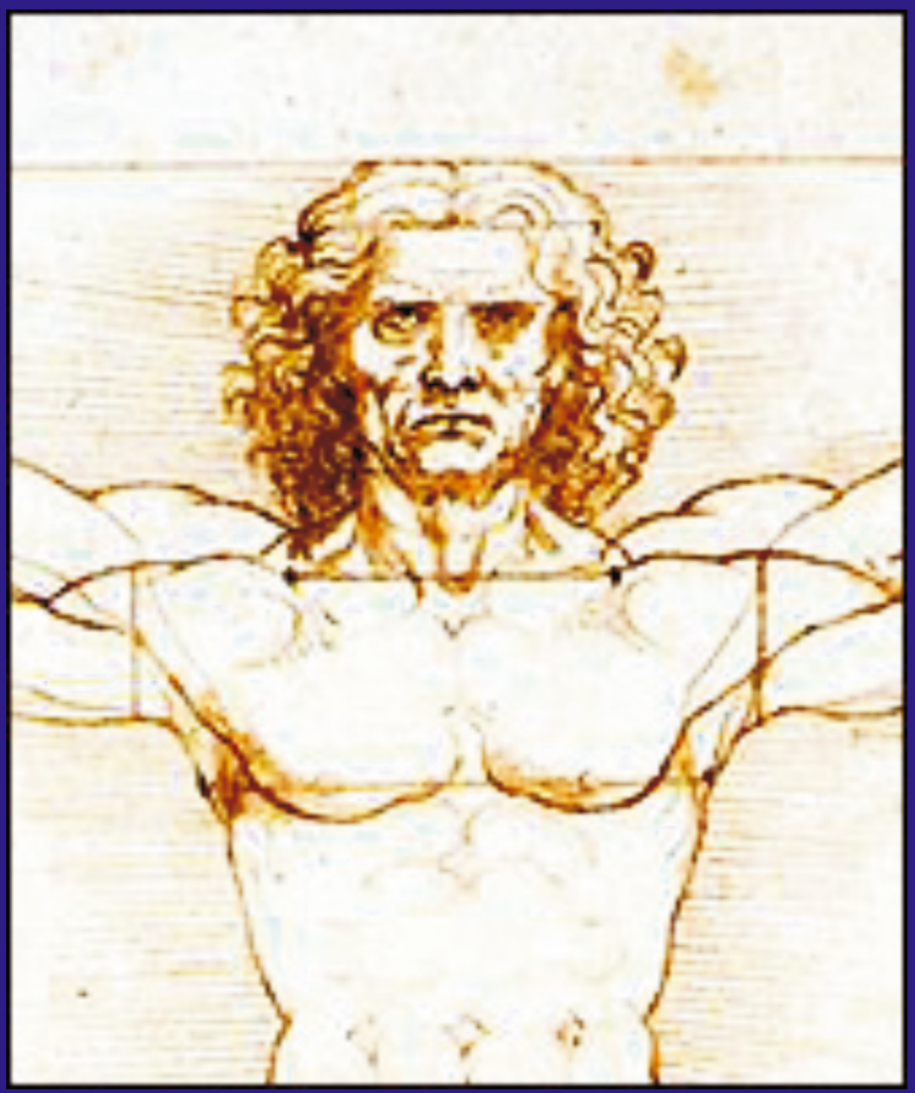

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SANAMED

Number 18(3)/2023

CONTENT

SANAMED

Number 18(3)/2023

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Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

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LABORATORY DIAGNOSIS OF ASCARIS LUMBRICOIDES INFESTATION IN PAEDIATRIC POPULATION IN TWO MUNICIPALITIES IN BOSNIA AND HERZEGOVINA

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Abstract: **Introduction:** *Ascaris lumbricoides* is a widely spread helminthic infection, predominantly affecting children, making them the most commonly infected population group. The objective of this study is to assess the prevalence of *Ascaris lumbricoides* infestation in two municipalities, Tešanj and Maglaj, and to investigate the occurrence of *Ascaris lumbricoides* infections in the pediatric population, focusing particularly on preschool children.

Materials and Methods: The study involved the collection of 1409 fecal samples from the Tešanj and Maglaj areas, gathered over a 6-month period, spanning from September 2018 to February 2019. The processing of these samples was conducted in the Microbiology Laboratory of Tešanj General Hospital.

Results: Out of the total 1409 samples, 129 (9.16%) tested positive for *Ascaris lumbricoides* infestation. In Tešanj, where 1198 samples were collected, 106 (8.85%) tested positive, while in Maglaj, 211 samples were collected, with 23 (10.9%) testing positive. Notably, the majority of positive cases in both Tešanj and Maglaj were preschool-age children, accounting for 88.68% and 86.96%, respectively. The study did not identify any statistically significant correlation between age and gender distribution among those with positive test results in either Tešanj or Maglaj.

Conclusion: Based on the study results, which have highlighted the infestation of preschool children with *Ascaris lumbricoides* in two municipalities in our country, it is imperative to implement preventive measures aimed at reducing the incidence of infection.

Keywords: *Ascaris lumbricoides*, Ascariasis, infestation, children.

INTRODUCTION

Ascaris lumbricoides is a parasitic nematode that causes ascariasis (1), the most prevalent helminthic infection affecting over 1.2 billion people globally (2). Its prevalence is particularly concentrated in tropical and subtropical regions with inadequate sanitation conditions, primarily affecting children (3). In 2018, over 676 million school-aged children in endemic countries received antihelminthic medications, covering 53% of children at risk (4).

Transmission occurs through the fecal-oral route, with risk factors including inadequate personal hygiene and sanitation, warm climates, and high humidity (5). Most individuals with intestinal ascariasis are asymptomatic. However, those who do exhibit symptoms commonly experience pulmonary or gastrointestinal issues such as nausea, bloating, reduced appetite, abdominal distension and discomfort, recurrent abdominal pain, and intermittent diarrhea (2). Prolonged infestation with *Ascaris lumbricoides* may lead to poor weight gain or malnutrition, potentially

impairing both physical growth and cognitive development over time (6).

Diagnosing of *A. lumbricoides* involves identifying parasite eggs, larvae, or adult worms. Stool sample examination using light microscopy remains the primary method to identify and quantify *A. lumbricoides* eggs. However, the uneven distribution of eggs in stool samples might yield false-negative results, particularly in cases of low-intensity infections or post-treatment. The standard treatments for ascariasis include albendazole, mebendazole, or ivermectin (7).

Aim

This study aims to evaluate the prevalence of *Ascaris lumbricoides* infestation in two municipalities, Tešanj and Maglaj. Additionally, it aims to investigate *Ascaris lumbricoides* infections among the pediatric population, specifically focusing on preschool children. *Our assessment involves examining the* infestation occurrence in these areas and analyzing its prevalence concerning gender, age, and place of residence.

MATERIALS AND METHODS

Specimen Collection

This study encompassed the collection of 1409 fecal samples from the Tešanj and Maglaj areas over a 6-month period, spanning September 2018 to February 2019. The samples were obtained and processed at the Microbiology Laboratory of Tešanj General Hospital.

In suspected cases of helminthiasis, it is essential to examine a minimum of 3 fecal samples, collected at intervals of 2 to 3 days. Each sample, weighing 10 grams, was obtained from both the surface and the depth of the fecal material and then delivered to the laboratory in specialized containers. Pertinent information, including the patient's name, surname, and the precise day and time of sample collection, was recorded for each specimen.

Liquid samples were analyzed within 30 minutes, while formed feces were examined within 2-3 hours post-collection. If necessary, formed samples could be studied within 24 hours if refrigerated at 4 ºC. For transportation purposes when immediate analysis wasn›t feasible, a preservative was added. A 5% buffered aqueous solution of formalin served as the preservative, effectively fixing the *Ascaris lumbricoides* eggs and larvae. There are also various commercially available kits for preserving fecal samples, comprising vials with preservatives (8).

Methods

The flotation technique and sedimentation methods belong to the category of concentrated methods. The main task of these methods is to separate the parasites from other elements in the fecal sample and to concentrate them, which enables easier detection. The flotation technique concentrates the parasites on the surface of the concentration solution, while the other elements of the fecal sample settle to the bottom of the test tube, precisely because of the differences in specific weights between the parasites and the solution used for concentration. There are two types of flotation techniques, with or without centrifugation, and zinc sulphate ($ZnSO_4$) and saturated salt solution (NaCl) can be used as flotation solutions.

In our study, the flotation method saturated with salt solution (NaCl) without centrifugation was used. After a sample of feces is taken from the examinee, a small amount is taken with a wooden stick in several places and dissolved in a saturated salt solution (NaCl), the specific gravity of which is 1.20.

Procedure

1. Emulsify 0.5 grams of feces in 2 to 3 ml of saturated NaCl solution within a test tube with a 15 mm inner diameter.

2. Fill the test tube with NaCl solution and mix well. Place the test tube in a vertical position in the test tube rack.

3. Add additional NaCl solution to fill the test tube to its brim.

4. Carefully cover the test tube with a cover glass.

5. Allow the solution to stand at room temperature for 30-45 minutes, allowing sufficient time for *Ascaris lumbricoides* eggs to rise to the surface.

6. Carefully lift the cover glass using tweezers, transfer it onto a microscope slide, and examine under a microscope.

The disadvantage of this method is that after 60 minutes the eggs of *Ascarislumbricoides* begin to settle at the bottom of the test tube, so it is necessary to make the slides within 30-45 minutes.

The results were processed using standard statistical methods using the SPSS Statistical Package for Social Sciences version 13.0 (Chicago, IL, USA). The results for independent continuous variables are expressed as absolute N and percentage values (%). The analysis of categorical variables' differences among observed groups employed either the Chi-square or Fisher's exact test. The value of $p < 0.05$ was taken as statistically significant.

RESULTS

Out of the 1409 samples analyzed, 129 (9.16%) yielded a positive result for *Ascaris lumbricoides* infestation, while the remaining 1280 (90.84%) were

negative. This difference was found to be statistically significant ($p < 0.001$).

Among the 1198 samples collected in Tešanj, 106 (8.85%) tested positive for *Ascaris lumbricoides* infestation. Within this group, 42.45% were males, and the remaining 57.55% were females. The majority of the samples 91.15%, yielded a negative result. In Maglaj, a total of 211 samples were collected, and 10.9% of these samples tested positive for *Ascaris lumbricoides* infestation. Among those with positive results, 73.91% were males, while the remaining 26.09% were females. 188 samples (89.1%) showed a negative result for *Ascaris lumbricoides* infestation. The determined difference in the gender distribution of respondents with a positive finding in relation to the surveyed municipalities was statistically significant ($p = 0.01$) (Figure 1).

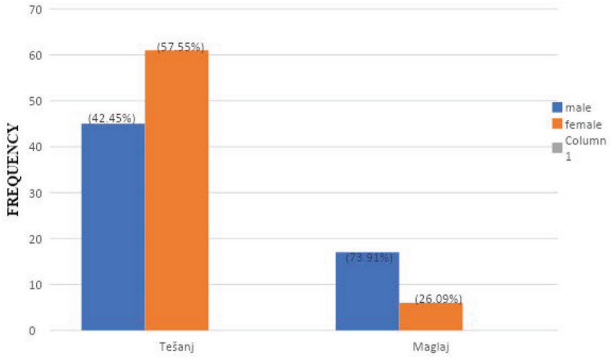

Figure 1. *Gender distribution of respondents with a positive findings in relation to the investigated municipalities*

Among the samples from Tešanj with a positive result for *Ascaris lumbricoides* infestation, 11.32% of them were of school-age, and the remaining 88.68% were preschool-age children. In the case of the 23 samples from Maglaj that tested positive, 13.04% of them belonged to the school-age group, while the remaining 86.96% were preschool-age children (Figure 2).

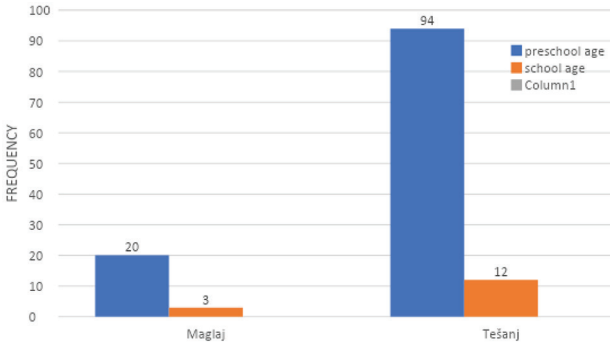

Figure 2. *Age distribution of respondents with a positive findings in relation to the investigated municipalities*

Among 106 examinees with a positive result from Tešanj, 20.75% were from urban areas, while the other 79.25% were from rural areas.

Out of a total of 106 respondents with a positive result from Tešanj, the frequency of male examinees of school age was 6.6%, and of preschool age 35.85%. The frequency of female examinees of school age was 4.72%, and of preschool age 52.83%. There was no statistically significant dependence between the age distribution and gender of examinees with a positive test in Tešanj ($p = 0.353$).

Among 23 samples with a positive result from Maglaj, the frequency of male examinees of school age was 8.7%, and 65.22% of preschool age. The frequency of female examinees of school age was 4.72%, and of preschool age 21.74%. There was no statistically significant dependence between age distribution and gender in examinees with a positive test in Maglaj ($p = 1.0$).

Out of the 106 samples with a positive result from Tešanj, the frequency of male examinees from urban areas was 8.49%, while from rural areas, it was 12.26%. For female examinees, the frequency from urban areas was 33.96%, and from rural areas, it was 45.28%. There was no statistically significant dependence between the regional distribution and gender of examinees with a positive test in Tešanj ($p = 0.896$).

The frequency of school-age examinees from urban areas among 106 positive samples from Tešanj, was 1.89%, and from rural areas 9.43%. The frequency of preschool examinees from urban areas was 18.87% and from rural areas 69.81%. No statistically significant dependence was found between age and regional distribution in examines with a positive test in Tešanj ($p = 0.340$).

DISCUSSION

Parasitosis is prevalent in tropical countries, with the highest number of cases reported in China, Southeast Asia, and the coastal regions of West and Central Africa. Annually, it affects more than one billion people globally, and over 60,000 cases result in fatalities (9). School-aged children are more susceptible to infestations compared to the adult population. Consequently, the World Health Organization has initiated control programs in endemic countries with a high prevalence of infestations. These programs are designed to decrease the number of infected individuals and minimize morbidity. Additionally, the World Health Organization has incorporated preschool children as a high-risk population in these programs because 10-20% of children in that age group are infested with *Ascaris lumbricoides* or other helminthes (10, 11).

In endemic countries, it is the most common cause of malabsorption and malnutrition in children, and it can also lead to disorders of growth, development, and

cognitive dysfunction. Given that *Ascaris* disrupts the absorption of vitamin A, in preschool children, this interference can result in clinical symptoms of vitamin A deficiency, increasing morbidity and mortality (12). A study conducted in Nepal revealed that the prevalence of xerophthalmia was three times greater in children between the ages of 6 and 120 months who were infested with *Ascaris lumbricoides*, in comparison to children who were not infested (13, 14).

In our study, 9.16% of the samples tested positive for *Ascaris lumbricoides*, and all individuals with positive fecal findings were either school-aged or preschool-aged children. Similar research conducted in South Asia reported similar findings (15).

In Tešanj and Maglaj, there were more positive findings of infestation with *Ascaris lumbricoides* among preschool-age children than among school-age children. A study conducted in Slovakia reported similar results (16). Conversely, somewhat different results were obtained by studies conducted in Sri Lanka and India, showing almost an equal number of infected individuals in both age groups (17, 18). By observing the increased prevalence of infestations in preschool children in our research, we can conclude that age affects the frequency of infestations.

A study conducted in Slovakia and China shows that infestations with *Ascaris lumbricoides* are more common in male examinees, correlating with the results of our research in the area of Maglaj compared to the data in the area of Tešanj (16, 19). Conversely, studies conducted in Sri Lanka and India showed that the prevalence of infestations was higher in female children (17, 18). The variations in gender distribution among the individuals who were infested can be attributed to inadequate personal hygiene in some subjects, as well as differences in the dietary habits of household members. Additionally, the significance of the water supply should not be discounted, as individual households are typically responsible for their own water sources, often relying on their private wells.

Regarding the total number of examinees with infestation caused by *Ascaris lumbricoides* from Tešanj, most of them were from rural areas compared to subjects from urban areas ($p < 0.001$). These results do not coincide with the results of research from Nicaragua, where there is a statistically significant difference in regional distribution, but in favor of respondents living in urban areas ($p = 0.004$) (20). The results of the regional distribution of Tešanj may differ from the results of other studies due to different systems of collection and removal of sanitary-fecal wastewater, where some households still use septic tanks while others are connected to the sewage network, which prevents the spread of infectious diseases.

Analyzing the collected data from the area of both municipalities, we conclude that there is no statistically significant difference in the frequency of infestations, nor is there a difference in the age distribution of subjects infested with *Ascaris lumbricoides*, in contrast to the gender distribution where a statistically significant difference is observed. The research confirmed that the prevalence of infestations in both municipalities is higher in the pediatric population of preschool-age compared to the school population, as well as that the prevalence of infestations is higher in rural areas of Tešanj compared to urban ones.

Understanding the factors contributing to the occurrence of infestations is crucial for implementing measures to reduce the number of infections and prevent complications, especially in children who are more vulnerable than the adult population. The preventive actions that should be undertaken include: enhancing sanitation conditions, improving access to clean water, educating the public about parasitic infections, emphasizing the significance of maintaining personal and communal hygiene, and discouraging the use of human feces in agriculture.

CONCLUSION

Ascariasis stands as a significant public health concern, demanding focused attention on high-risk groups and ensuring access to improved water, sanitation, and hygiene facilities. Given that the findings of our study have revealed the infestation of preschool children with *Ascaris lumbricoides*, it is essential to implement preventive measures aimed at reducing the incidence of infection. In conclusion, heightened awareness and knowledge about *A. lumbricoides* infection, among both healthcare professionals and the general public, are imperative. This will enhance the clinical detection and management of cases, as well as public health control measures.

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Sažetak

LABORATORIJSKA DIJAGNOSTIKA ASCARIS LUMBRICOIDES INFESTACIJE U PEDIJATRIJSKOJ POPULACIJI U DVE OPŠTINE U BOSNI I HERCEGOVINI

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Uvod: *Ascaris lumbricoides* je najčešći uzrok helmintičkih infekcija u svetu, a prvenstveno pogađa decu, što ih čini najčešće zaraženom populacionom skupinom. Cilj ovog istraživanja je proceniti prevalenciju infestacije *Ascaris lumbricoides* u dve opšine, Tešanj i Maglaj, te istražiti pojavu infekcija *Ascaris lumbricoides* u pedijatrijskoj populaciji, sa posebnim fokusom na decu predškolskog uzrasta.

Materijali i metode: Istraživanjem je prikupljeno 1409 uzoraka stolice sa područja Tešnja i Maglaja. Ovi uzorci su prikupljani u periodu od 6 meseci, od septembra 2018. do februara 2019. godine. Obrada uzoraka obavljena je u Mikrobiološkoj laboratoriji Opste bolnice Tešanj.

Rezultati: Od ukupno 1409 uzoraka, 129 (9,16%) je bilo pozitivno na infestaciju *Ascaris lumbricoides-om*. U Tešnju, gde je prikupljeno 1198 uzoraka, pozitivno je bilo 106 (8,85%). U Maglaju je prikupljeno 211 uzoraka, a 23 (10,9%) su imala pozitivan nalaz. Većina pozitivnih uzoraka u Tešnju i Maglaju bila su deca predškolskog uzrasta, 88,68%, odnosno 86,96% respektivno. Studija nije utvrdila nikakvu statistički značajnu korelaciju između dobne i polne distribucije među onima sa pozitivnim rezultatima testa niti u Tešnju, ni u Maglaju.

Zaključak: U svetlu rezultata našeg istraživanja, koji su ukazali na infestaciju dece predškolskog uzrasta *Ascaris lumbricoides*-om u dve opštine u našoj zemlji, neophodno je sprovesti preventivne mere s ciljem smanjenja incidencije infekcije.

Ključne reči: *Ascaris lumbricoides*, Ascariasis, infestacija, deca.

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Original article

BIOELECTRICAL IMPEDANCE ANALYSIS OF BODY COMPOSITION IN FITNESS AND BODYBUILDING COMPETITORS AND RECREATIONAL EXERCISERS

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Abstract: **Introduction**: Bodybuilding and fitness are sports in which the primary goal is to build and shape a desirable body figure. Consequently, achieving the ideal body composition is the ultimate aspiration of every participant in these sports. Body composition analysis is a valuable tool for assessing body structure and quantifying data for this specific athletic population. **The aim** of this study was to determine and compare the body composition characteristics of fitness and bodybuilding exercisers, both competitive and recreational.

Material and Methods: This study included 89 adult women and men, aged 18 to 37, who were categorized into four groups: female competitors (N = 9), female recreational participants (N = 30), male competitors (N = 15), and male recreational participants (N = 35). Body composition was assessed using the bioelectrical impedance method, specifically the InBody720.

Results: The comparison of bioelectrical impedance analysis (BIA) obesity parameters revealed that BMI did not significantly differ between competitors and recreational participants in both male and female groups. However, competitors (both male and female) displayed a higher volume of body fluids (ICW and ECW). Body fat mass (BFM) was statistically greater in recreational participants when compared to competitors, with females having 18.58 kg vs. 12.47 kg, and males having 16.64 kg vs. 9.81 kg. Mean values of body fat percentage were also statistically higher in recreational participants compared to competitors, with women at 27.25% vs. 16.39% and men at 19.49% vs. 11.97%.

Conclusions: Fitness competitors had a significantly higher fat-free mass and a significantly lower fat component. Recreational exercisers exhibited significantly higher obesity parameters, body fat percentage, and waist-to-hip ratio (WHR) compared to competitors in fitness and bodybuilding.

Keywords: bodybuilding, body fat mass, competitors, fitness, recreational, skeletal muscle mass.

INTRODUCTION

Bodybuilding and fitness are sports focused on achieving a desirable body figure, making optimal body composition the ultimate goal for competitors in these disciplines. The criteria for required muscle mass and body fat levels vary among competitive categories within fitness (1). Competitive bodybuilding assesses the visual presentation of muscle mass, symmetry, muscle definition, and overall physique. The sport primarily emphasizes achieving 'aesthetic' muscle hypertrophy (2). It demands rigorous, years-long training to develop muscular shape, size, definition, and symmetry. During the off-season, many bodybuilders increase their body mass and fat to facilitate lifting heavy weights and intensifying training for muscle mass gains (3, 4). This phase of muscle hypertrophy is succeeded by a shorter phase called muscle definition, wherein subcutaneous fat deposits are reduced, and exercises are aimed at enhancing muscle bundle separation, resulting in an improved visual presentation (5).

Competitors with the lowest body fat percentage, often referred to as the 'leanest,' tend to receive higher rankings. The second crucial factor is muscularity, where competitors with comparable muscle development favor those displaying greater muscle definition. Additionally, proportionality plays a pivotal role; well-developed chest and arm muscles, coupled with a narrow waist, contribute significantly to an appealing body shape among competitors (6).

The primary distinction between recreational and competitive exercisers in various sports, including fitness and bodybuilding, lies in the ultimate objective of their physical activities. Exercise is characterized as planned, regular, repetitive, and structured physical activity (7). When exercise aims to maintain and/or enhance overall health and fitness, it falls under the recreational category (8). Conversely, if the purpose is competition, the physical activity is classified as a sport. Physical activities for competitive purposes typically involve significantly higher volume compared to recreational activities (9).

The current epidemic of physical inactivity and increased awareness of the importance of regular physical activity have led to a surge in individuals engaging in recreational fitness. Moreover, an expanding number of exercise enthusiasts are venturing into the realm of competitive fitness and bodybuilding. Utilizing body composition analysis as a valuable and effective tool for assessing body structure and morphological components allows gathering data for this population of athletes (3).

The aim of this study is to determine and compare the body composition characteristics of fitness and bodybuilding exercisers, both competitive and recreational. Our hypothesis suggests that competitors will exhibit higher fat-free mass and subsequently lower obesity parameters compared to recreational participants.

MATERIAL AND METHODS

Participants

Participants were recruited from the 'Atleta Bodybuilding and Fitness Center' in Skopje, North Macedonia. The study involved 89 adults aged 18 to 37, with a mean age of 26 ± 5.1 years. They were divided into four groups: female competitors (n = 9), female recreational participants (n = 30), male competitors (n = 15), and male recreational participants (n = 35). Competitors had engaged in at least one bodybuilding or fitness competition within the past 12 months; females participated in fitness categories, while males competed in bodybuilding categories. Recreational participants had committed to regular resistance training for a minimum of 12 months, averaging 3 to 5 sessions per week.

Procedure

The body composition analysis took place at the Institute of MEP Physiology and Anthropology, Faculty of Medicine, Skopje, Republic of North Macedonia. This study received approval from the Faculty of PESH, UKIM, Ethical Committee (2021/08-121) and was conducted in adherence to the Code of Ethics of the World Medical Association, also known as the Declaration of Helsinki.

Methods

Height measurements were obtained using a stadiometer, while body mass was recorded using an electronic weighing scale. To assess the body composition of the subjects, bioelectrical impedance analysis (BIA) was performed using the InBody 720 device. This non-invasive technique involves emitting a very low multi-frequency current and measuring the resistance to current flow through various body parts and tissues.

The BIA method considers that tissues with high fluid and electrolyte content, such as blood, conduct electricity well, while fatty tissue and bones impede the electrical signal's conduction. This allows for an assessment of tissue composition.

While the BIA device offers a wealth of information about body composition, this study specifically analyzed the following parameters:

- Body weight (BW)
- Body mass index (BMI)
- Body fluids: intracellular water (ICW) and extracellular water (ECW)
- Protein and mineral components
- Body fat percentage (BF%)
- Body fat mass (BFM)
- Skeletal muscle mass (SMM)
- Waist-to-hip ratio (WHR)
- Soft lean mass (SLM)
- Fat-free mass (FFM)

Data analysis

The analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23.0. For all variables examined, the following statistical parameters were calculated: Arithmetic means (X), Standard deviations (SD), Minimum scores (min), Maximum scores (max), Skewness to assess the distribution of results, Kurtosis to evaluate the distribution of results, The Kolmogorov-Smirnov test (according to Liliefors) to test the normality of the result distribution, Differences in anthropometric variables were determined through analysis of variance (ANOVA). The level of statistical significance was set at $p < 0.05$.

RESULTS

The variables derived from anthropometry and BIA analysis are categorized for male and female par-

ticipants, and divided into subgroups based on their training levels in recreation and competition.

Table 1 presents descriptive statistics for the anthropometric indicators of competitive and recreational women. A comparison of height between female competitors and recreational women revealed a statistically significant difference in favor of female competitors (170.9 cm vs. 164.7 cm). However, there was no statistically significant difference in weight between recreational women and competitive women (62.3 kg vs. 62.5 kg).

The difference in body mass index (BMI) between recreationally exercising men and competitive men was not statistically significant (25.86 vs 25.81). A similar pattern was observed in the female group (23.03 vs 22.51). Female competitors displayed sig-

Table 1. *Descriptive statistics for BIA indicators in the group of women: recreational and competitive*

	Women recreationists			Women competitors			Sig.
	Mean ± SD	min	max	Mean ± SD	min	max	p
Height * (cm)	164.73 ± 5.87	155.0	179.0	170.89 ± 6.2	164.0	182.0	0.005
Weight (kg)	62.54 ± 10.16	49.0	87.6	62.27 ± 7.5	55.0	76.0	0.943
BMI (kg/m^2)	23.03 ± 3.91	18.6	34.2	22.51 ± 2.5	20.8	28.0	0.659
ICW * (l)	20.23 ± 1.93	17.2	24.9	23.45 ± 3.1	20.0	28.6	0.010
ECW * (l)	12.36 ± 1.19	10.3	15.5	14.23 ± 1.8	12.2	17.5	0.009
Protein * (kg)	8.79 ± 0.83	7.4	10.8	10.17 ± 1.5	8.6	12.8	0.041
Mineral * (kg)	3.22 ± 0.36	2.7	4.1	3.81 ± 1.1	2.9	6.6	0.009
BFM * (kg)	18.58 ± 8.67	6.3	40.4	12.47 ± 5.4	3.7	23.0	0.027
SMM * (kg)	24.4 ± 2.29	20.4	29.9	29.03 ± 4.3	24.0	37.4	0.019
BF% *	27.25 ± 9.09	12.5	46.1	16.39 ± 2.7	13.4	21.8	0.000
WHR	0.87 ± 0.07	0.8	1.0	0.83 ± 0.04	0.8	0.9	0.117
SLM * (kg)	41.93 ± 3.79	35.4	51.1	49.23 ± 8.2	41.3	66.4	0.003
FFM * (kg)	44.51 ± 4.04	37.6	54.3	52.22 ± 8.7	43.9	70.4	0.002

BMI – body mass index; ICW – Intracellular water; ECW – extracellular water; BFM – body fat mass; SMM – skeletal muscle mass; BF% - body fat percent; WHR – waist to hip ratio; SLM – soft lean mass; FFM – fat free mass; * - statistically significant difference ($p < 0.05$)

Table 2*. Descriptive statistics for BIA indicators in the group of men: recreationists and competitors*

	Men recreationists			Men competitors			Sig.
	Mean ± SD	min	P	Mean ± SD	min	max	p
Height (cm)	178.60 ± 4.9	168.0	188.0	177.23 ± 6.1	165.5	187.0	0.430
Weight (kg)	82.78 ± 10.5	61.8	105.0	81.04 ± 10.6	62.6	97.8	0.578
BMI (kg/m^2)	25.86 ± 2.7	20.8	34.1	25.81 ± 2.1	22.4	29.4	0.955
ICW (l) *	30.06 ± 3,4	23.8	37.5	33.03 ± 4.5	24.4	39.8	0.003
ECW (l) *	17.55 ± 1.9	13.9	22.1	19.54 ± 2.4	14.4	22.8	0.001
Protein (kg)	13.62 ± 2.2	10.3	19.3	14.35 ± 1.9	10.6	17.2	0.179
Mineral (kg) *	4.43 ± 0.5	3.4	5.6	4.81 ± 0.7	3.4	5.8	0.037
BFM (kg)*	16.64 ± 7.3	5.1	35.0	9.81 ± 2.9	3.7	14.6	0.003
SMM (kg)*	37.48 ± 6.5	29.0	65.6	40.71 ± 5.7	29.9	49.9	0.043
PBF% (kg)*	19.49 ± 6.5	8.1	34.8	11.97 ± 3.5	5.3	20.0	0.001
WHR (kg)*	0.90 ± 0.1	0.8	1.2	0.82 ± 0.05	0.7	0.9	0.001
SLM (kg)*	60.75 ± 7.0	48.5	76.8	70.41 ± 7.3	61.8	80.7	0.000
FFM (kg) *	64.49	51.3	81.3	75.19 ± 7.4	65.3	85.5	0.000

BMI – body mass index; ICW – Intracellular water; ECW – extracellular water; BFM – body fat mass; SMM – skeletal muscle mass; BF% - body fat percent; WHR – waist to hip ratio; SLM – soft lean mass; FFM – fat free mass; * - statistically significant difference ($p < 0.05$)

nificantly higher amounts of intracellular and extracellular water (ICW: 23.5 liters vs. 20.2 liters; ECW: 14.2 liters vs. 12.3 liters). Moreover, female competitors exhibited higher levels of the protein component (10.2 kg vs. 8.8 kg) and mineral component (3.8 kg vs. 3.2 kg). Skeletal muscle mass (SMM), lean body mass, and soft lean mass (SLM) were significantly higher in female competitors compared to recreational women.

Regarding body fat, recreational women had higher levels in kilograms (18.6 kg vs. 12.5 kg), while female competitors had significantly lower body fat percentage (16.4% vs. 27.3%). However, the waist-to-hip ratio did not show a statistically significant difference between the two groups (0.83 vs. 0.87).

Table 2 displays descriptive statistics and significant differences in anthropometric indicators obtained by BIA analysis among male respondents, including competitors and recreational exercisers. Both male groups, competitors and recreationists, showed similar average height (177.2 cm vs. 178.6 cm) and weight, with no statistically significant difference. BMI values did not significantly differ between men exercising recreationally and those who competed (around 25.8).

Male competitors demonstrated significantly higher amounts of body water (ICW = 33.3 liters vs. 30.05 liters; ECW = 19.5 liters vs. 17.5 liters) and a higher mineral component (4.8 kg vs. 4.4 kg). In contrast, recreational male participants had higher body fat in kilograms (16.6 kg vs. 9.8 kg) and a higher body fat percentage (19.5% vs. 11.9%) compared to male competitors.

DISCUSSION

The study aimed to explore morphological characteristics using bioelectrical analysis of body composition in individuals engaged in fitness or bodybuilding, either recreationally or competitively.

Analysis of female fitness competitors revealed optimal body composition, with a lean component (FFM) constituting approximately 84% of their total body mass. Their skeletal muscle mass accounted for about 47% of their total weight, signifying well-developed musculature. Female competitors maintained an average body fat percentage of 16%, showcasing their fitness. In contrast, recreational female athletes, despite similar average weight and normal BMI, displayed a high average body fat percentage of around 27%, indicating a wider range of values (ranging from 16% to 46%). Their relative lean body mass and skeletal muscle mass were 71% and 39%, respectively.

In the case of male fitness competitors, an analysis of their body composition showed that they had a normal body mass index but were near the upper limit (BMI = 25.08) due to a notably high lean component. The average muscle mass accounted for approximately 50% of their total weight. The fat component was at the lower end of BIA values for healthy, inactive individuals, and was appropriate for fitness athletes, averaging around 12% (ranging from 5% to 20%). The thickest skinfold measurement among the competitors was observed on the thigh, while the thinnest was on the forearm.

For recreational exercisers, an analysis of their body composition indicated an average value of the body mass index slightly above the upper limit of normal values (BMI = 25.8). The average body fat percentage was approximately 19%, which falls within the normal BIA values (ranging from 15% to 20%). The relative value of lean body mass and skeletal muscle mass was 78% and 45%, respectively.

In the realm of competitive bodybuilding, the lack of adipose tissue, or a low percentage of the fat component, is a sought-after characteristic. Competitors often employ nutritional strategies to reduce body fat well below normal levels, frequently not exceeding 7% (10, 11). A study of anthropometric traits in professional and amateur bodybuilders in Poland revealed that professionals typically had larger limb circumferences and smaller skinfold sizes. BMI was significantly higher in professionals, while body fat percentage was notably higher in amateurs, measuring 10.67% vs. 20.05%, as determined by BIA (12).

According to the recommendations of the American College of Sports Medicine (ACSM), the optimal representation of adipose tissue in athletes should be around 12%. It's important to note that this recommendation is relatively general because different types of sports, based on their physical demands, result in varying body compositions in athletes (13). Notably, bodybuilders in the immediate pre-competition phase often showcase extremely low body fat levels, well below the recommended ranges for healthy sedentary individuals (10-20% for men and 15-25% for women according to the BIA method). This drastic reduction in body fat is a characteristic strategy observed in bodybuilders as they approach competition, emphasizing the aesthetic aspect of their physique over standard health-related guidelines.

Numerous studies on body fat percentage in bodybuilders from different countries have consistently shown very low body fat percentages. For instance, in the USA in 1992 (14), men in 1990 had 6.0 ± 1.8% body fat, and women had 9.8 ± 1.5% (15). In Great Britain, body fat percentages ranged from 4.1% to 10.9% (16), and in Poland, men had 5.68% body fat according to skinfold measurements or 10.67% according to the BIA method (12). A study in Brazil found that male

physique competitors had body fat percentages of 4% and 8.6%, while in the wellness category, percentages of 17.3% and 8.9% were observed (17).

During competitions, the representation of adipose tissue in the body composition of bodybuilders typically ranges from 3% to 6% in men and 9% to 12% in women (18). This extremely low body fat percentage is necessary for achieving good muscle separation and definition, which is a crucial factor for successful performance and placement in both bodybuilding and fitness competitions (19).

Morphological characteristics and body composition have been analyzed in bodybuilders in relation to different phases of training. In one of the initial studies on this topic, where body mass was estimated using the Brozek anthropometric method, it was found that during the off-season, bodybuilders had a body fat percentage of 9.7 ± 3.1%, whereas during the competitive season, their body fat percentage dropped to 5.9 ± 3.2%. The change in female bodybuilders was from a body fat percentage of 16.8 ± 4.5% in the off-season to 9.5 ± 3.5% during competition. Furthermore, the subjects in this study experienced a slight decrease in lean body mass, with men going from 82.7 kg to 81.1 kg and women from 48.5 kg to 47.4 kg (20).

An examination of eating habits and self-perception among 120 bodybuilders from Turkey, divided into two groups, competitors and non-competitors, revealed the following morphological characteristics: Fat-Free Mass Index (FFMI) was 24.09 ± 3.05 kg/m^2 for competitors and 21.18 ± 1.93 kg/m^2 for non-competitors. The percentage of fat tissue in the entire group was 13.57 ± 4% (21). An analysis of Tunisian weightlifters showed that they had a BMI of 21.5 ± 3.35, body fat percentage (BF%) of 12.28 ± 5.22, and lean body mass (LBM) of 87.73 ± 5.22 kg (22). Heyward's research in 1989 compared the body composition of recreational and professional athletes, revealing that in men, the percentage of fat tissue was 9.7% for recreational athletes and 5.9% for professionals, while in women, it was 16.85% for recreational athletes and 9.5% for professionals (20).

A case study of a natural bodybuilder tracked changes in the cardiovascular system, body composition, muscle strength, and blood parameters over 12 months, including 6 months pre-competition and 6 months post-competition. During the pre-competition period, fat tissue decreased from 14.8% to 4.5% and then returned to the initial value of 14.6%. Muscle strength, blood pressure, and heart rate all decreased. Psychometric parameters of mood disturbance increased from 6 to 43 units during the preparation period and then corrected to 4 units during the 6-month post-competition period (23). In another case study of a natural bodybuilder, a 21-year-old Englishman reduced his body fat percentage from 14.8% to 6.8% during 14 weeks of training. Muscle strength showed a slight decline, while the mood swing test showed no significant difference (24).

Physique competitions are sporting events in which aesthetic appearance and posing ability are prioritized over physical performance. Female physique competitors are required to have a very lean body mass (LBM) and an extremely low fat component for the competition. Achieving this requires competitors to reduce their energy intake over an extended period, followed by intensive training regimes that result in a sudden weight loss at the end of the pre-competitive phase (25). In a study on the anthropometric profile of five elite Australian female bodybuilders, it was found that 12 weeks before the competition, the percentage of fat tissue determined by the densitometric method (DEXA) was 18.9 ± 4.6%, and 24 hours before the competition, it reduced to 12.4 ± 4.6%. The thickest skinfold measurement was on the front of the thigh, measuring 19.8 ± 5.1 mm, and before the competition, it decreased to 13.3 ± 3.2 mm. In this group of female bodybuilders, the mesomorphic somatotype dominated, followed by the endomorphic and least ectomorphic (26).

While published data in the field of anthropometry and body composition analysis may vary due to different techniques used, the majority of reports concur that bodybuilding and fitness competitors, both male and female, achieve exceptionally low values of body fat.

CONCLUSIONS

The majority of our participants, whether they were recreational exercisers or competitors, exhibited body components within the normal range for a healthy population. Fitness competitors displayed a significantly higher fat-free (muscle) component and a notably lower body fat component. In contrast, recreational exercisers had significantly higher obesity-related parameters, including BMI, body fat percentage (BF%), and waist-to-hip ratio (WHR), compared to their counterparts in fitness and bodybuilding competitions. The body composition parameters obtained through bioelectrical impedance analysis proved to be sensitive indicators of differences between the two studied groups, competitors and recreational exercisers.

Considering the comprehensive findings of this research, it can be concluded that engaging in fitness activities positively influences body composition. This effect is characterized by the optimization of body components, such as an increase in muscle mass and the maintenance of the fat component within desired

limits. Those who participate in competitive activities in the fields of bodybuilding and fitness tend to achieve the ideal body components, particularly a high muscle component and lower fat component.

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Sažetak

ANALIZA TELESNOG SASTAVA POMOĆU BIOELEKTRIČNE IMPEDANSE KOD FITNES I BODIBILDING TAKMIČARA I REKREATIVACA

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Uvod: Bodibilding i fitnes su sportovi u kojima je primarni cilj izgraditi i oblikovati željeni telesni izgled. Shodno tome, postizanje idealne telesne kompozicije je krajnja aspiracija svakog učesnika u ovim sportovima. Analiza telesne kompozicije je vredan alat za procenu strukture tela i kvantifikaciju podataka za ovu specifičnu sportsku populaciju. Cilj ovog istraživanja bio je da se utvrde i uporede karakteristike telesne kompozicije vežbača fitnesa i bodibildinga, kako konkurentnih tako i rekreativnih.

Materijal i metode: U ovo istraživanje bilo je uključeno 89 odraslih žena i muškaraca, uzrasta od 18 do 37 godina, koji su bili kategorizovani u četiri grupe: ženski takmičari (N = 9), ženski rekreativni učesnici (N = 30), muški takmičari (N = 15) i muški rekreativni učesnici (N = 35). Telesna kompozicija je procenjena korišćenjem metode bioelektrične impedancije, posebno uređajem InBody720.

Rezultati: Poređenje parametara gojaznosti bioelektričnom impedancijom (BIA) pokazalo je da indeks telesne mase (BMI) nije značajno razlikovao takmičare i rekreativne učesnike, kako kod muškaraca tako i kod žena. Međutim, takmičari (i muški i ženski) su pokazali veći volumen tečnosti u telu (ICW i ECW). Masno tkivo tela (BFM) je bilo statistički veće kod rekreativnih učesnika u poređenju sa takmičarima, pri čemu su žene imale 18,58 kg naspram 12,47 kg, a muškarci 16,64 kg naspram 9,81 kg. Srednje vrednosti procenta telesne masti su takođe statistički bile više kod rekreativnih učesnika u poređenju sa takmičarima, pri čemu su žene imale 27,25% naspram 16,39%, a muškarci 19,49% naspram 11,97%.

Zaključak: Takmičari u fitnesu imali su značajno veću masu bez masti i značajno niži procenat masnog tkiva. Rekreativni vežbači su pokazali značajno više parametre gojaznosti, procenat telesne masti i odnos struka i bokova (WHR) u poređenju sa takmičarima u fitnesu i bodybuildingu.

Ključne reči: bodibilding, telesne masti, takmičari, fitnes, rekreativci, skeletna mišićna masa.

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Case report

HEPATIC METASTASIS OF THYMOMA: CASE REPORT OF A FAST-GROWING ABDOMINAL MASS IN A PREGNANT PATIENT

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Abstract: **Introduction:** Thymomas are the most common primary mediastinal tumors originating from epithelial cells of the thymus, demonstrating epithelial differentiation. Pathologically, thymomas exhibit relatively slow growth and typically spread directly, with extremely rare occurrences of distant dissemination to extrathoracic organs. The precise incidence of such dissemination remains unknown. Distant metastases, particularly to the liver, are exceptionally rare, with only a few cases documented in the literature.

Case Report: A 39-year-old woman, in her 31st week of gestation, presented with abdominal pain and discomfort. She underwent ultrasonography, followed by an urgent MRI of the abdomen due to a protruding tumor mass in the liver. Shortly after delivering a healthy baby via cesarean section, she was admitted to the hospital for a CT scan of the abdomen. The imaging revealed multiple focal changes in the liver parenchyma, exhibiting radiological characteristics consistent with focal nodular hyperplasia. Less likely differential diagnoses included adenomas or hemangiomas. Subsequently, she underwent staged hepatectomy, and the results of the pathological analysis confirmed the presence of type B thymoma metastases in the liver.

Conclusion: According to the available data in the literature, metastatic thymomas are often identified in patients who have previously undergone treatment for the primary disease. Our patient did not have a history of thymectomy, as confirmed by postoperative chest scans. Onset of symptoms during late pregnancy guided our diagnosis, relying on overall clinical and radiological findings of the detected tumor. Our treatment involved staged hepatectomy post-childbirth, followed by adjuvant chemotherapy. Further comprehensive studies are essential to precisely understand neoplasm behaviors like thymoma for timely detection and effective treatment.

Keywords*:* thymoma, metastasis, liver, pregnancy, surgery.

INTRODUCTION

The thymus, a solid organ situated in the anterior superior mediastinum, contains both lymphoid and epithelial components (1, 2). Thymomas, originating from epithelial cells of the thymus, exhibit relatively slow growth and typically spread directly, with an extremely rare incidence of distant dissemination to extrathoracic organs, though the exact frequency remains uncertain (2). Distant metastases, especially to the liver, are exceptionally rare, with few documented cases in the literature (3, 4). The 2021 "World Health Organization (WHO) Classification of Thoracic Tumours" primarily categorizes thymomas, epithelial tumors of the thymus, based on cytomorphology. Benign cytomorphology types include A, AB, B1, B2, and B3, while malignant types correspond to thymic carcinoma, formerly categorized as type C (1, 5). Metastases are predominantly found in the pleural space, lung parenchyma, or bones, and are more commonly observed in patients previously treated for the primary tumor (6, 7). Liver metastases often remain asymptomatic, discovered incidentally or when the tumor mass ruptures, leading to emergencies like hematoperitoneum (8 ,9).

We present the case of a pregnant woman with a metastatic thymic tumor in the liver, exhibiting rapid growth in the third trimester of pregnancy, causing abdominal pain. This initiated further examination and led to the final diagnosis, without a history of previous thymectomy.

CASE REPORT

Our patient, a 39-year-old woman in her 31st week of pregnancy, visited the Clinic for Emergency Sur-

gery, University Clinical Centre of Serbia in Belgrade in May 2023 for an ambulatory examination, referred by her gynecologist due to upper abdominal pain as the primary complaint. During the initial visit, a routine ultrasound revealed a solid-cystic mass measuring 80 x 50 mm in the left liver lobe, exerting pressure on the stomach. Basic blood tests showed normal results, and she was subsequently referred to a gastroenterologist. Upon mutual agreement among the surgeon, gastroenterologist, and gynecologist, a follow-up ultrasound of the abdomen was scheduled for the following day. This examination, conducted by the same radiologist,

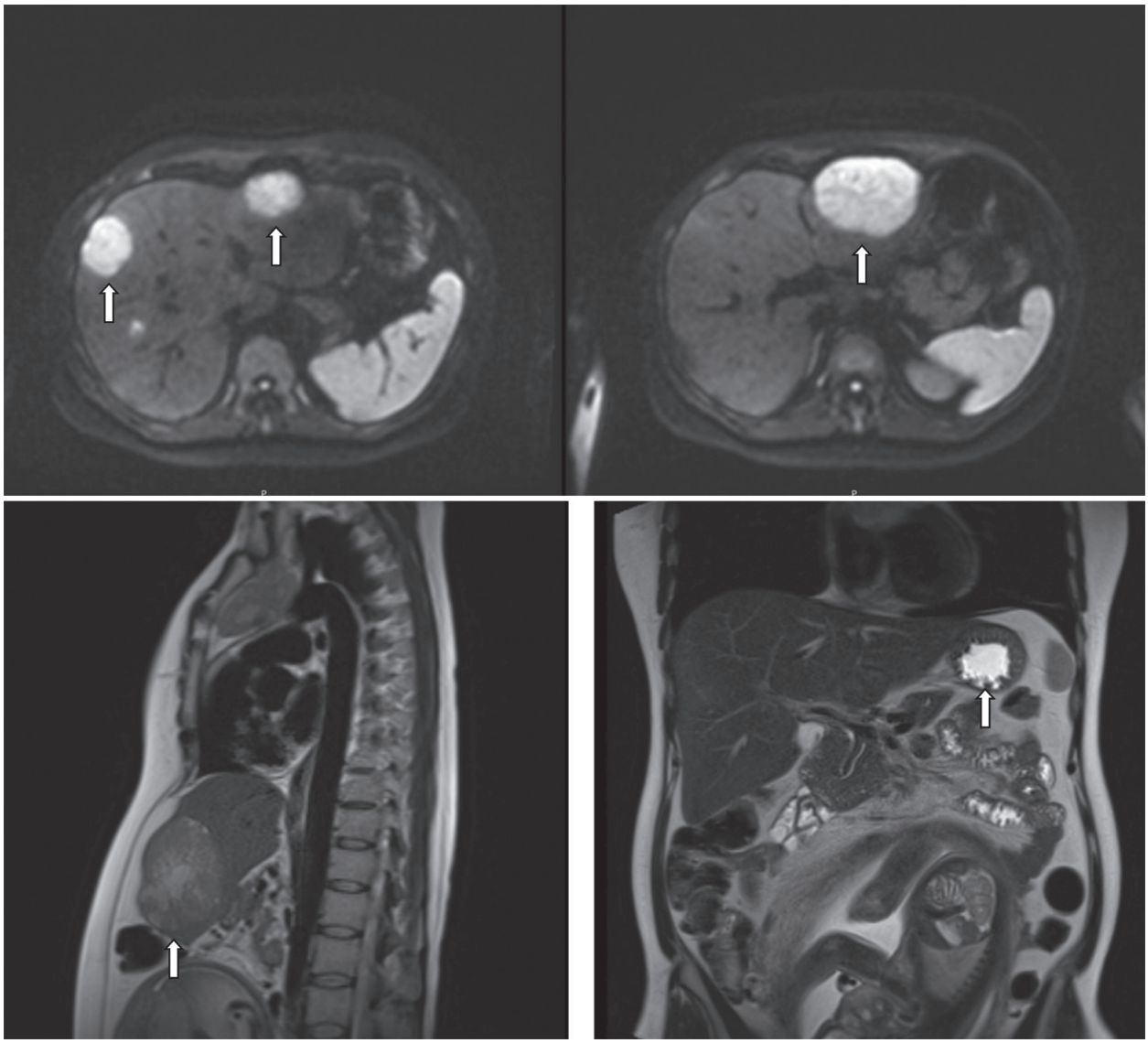

Figure 1. *Preoperative MRI of abdomen – white arrow indicates the tumor masses*

Figure 2. *Preoperative CT of abdomen - white arrow indicates the tumor masses*

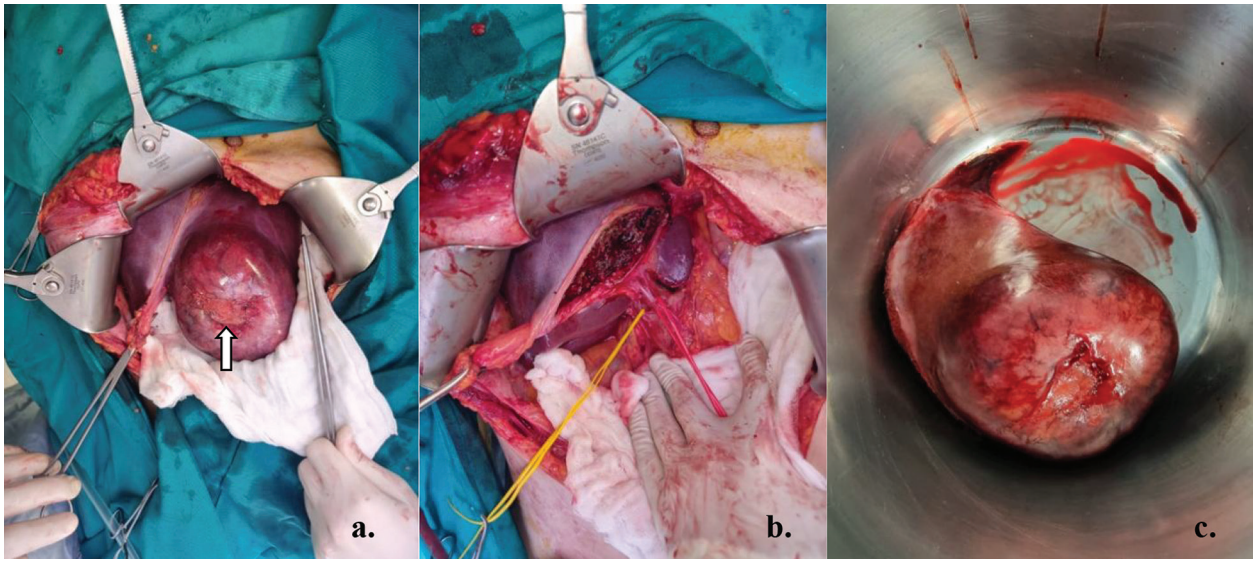

Figure 3. *Intraoperative finding – white arrow indicates the biggest tumor mass in left liver lobe a. Before the resection; b. After the resection; c. Resected tumor mass*

revealed a discreet increase in the size of the tumor mass. An urgent MRI examination of the abdomen and pelvis was promptly recommended. The MRI revealed several focal changes in the liver parenchyma, with the largest mass measuring 79 x 60 mm, subcapsular and positioned between the II and III segments. Additional masses were noted at the transition between the VIII and V segments (39 mm), within the V segment itself (15 mm), and one isolated in the VIII segment (12 mm). These findings exhibited radiological characteristics initially suggestive of focal nodular hyperplasia, with adenomas or hemangiomas considered less likely (Figure 1).

After a brief hospital stay, the patient was discharged in good general condition and had regular ultrasound follow-ups. Shortly after, she delivered a healthy child via caesarean section. Over the subsequent four weeks post-delivery, the size of the largest mass remained unchanged during weekly ultrasound examinations. Throughout the follow-up period, tumor marker values consistently remained within the reference range. However, due to the recurrence of pain, the patient was readmitted to the hospital, where an abdominal CT scan was conducted, prompting a recommendation for surgical intervention (Figure 2).

In July 2023, after appropriate preoperative preparation, a simultaneous resection of the II and III segments of the liver, along with the tumor mass located at the junction of the VIII and V segments, and the isolated tumor mass in the V segment was performed. Considering the remaining liver volume, it was decided during the surgery to postpone the resection of the remaining tumor mass until further histopathological findings were available (Figure 3).

The patient recovered well following the surgery and was discharged home. Pathohistological analysis revealed liver metastases originating from type B thymoma. About six weeks post-operation, a follow-up CT scan of the abdomen, small pelvis, neck, and chest was conducted, identifying the persistent tumor in the liver with unchanged dimensions. Additionally, a neoplastic alteration in the thymus measuring 88x55x57 mm was detected, accompanied by secondary deposits in the lung parenchyma and mediastinal lymph nodes. Subsequently, the case was presented to the oncology board, leading to further treatment decisions by the lymphoma tumor board and the thoracic surgeon.

Verbal and signed consent from the patient was obtained for the publication of this case report. All procedures conducted adhered to the principles outlined in the 1964 Helsinki declaration and its subsequent amendments.

DISCUSSION

Metastatic thymomas are mostly expected in patients previously treated for the primary disease (1, 2, 3). Khandelwal et al. reported hepatic metastasis of thymoma in about 4.8% of 62 thymoma cases (10). In our case, the initial examination detected the metastatic disease due to the expanding mass pressing on the liver capsule, causing abdominal pain during advanced pregnancy, coinciding with symptom onset. Considering the patient's medical history and the absence of a prior thymectomy, our case becomes more intriguing. Mallick J et al., in a literature review, noted 39 cases of thymoma with metastases beyond the thorax since the 1999 WHO Classification of Thoracic Tumours (1). Kim HJ et al. mentioned preoperative chemotherapy,

while Utsunomiya T et al. opted for radical surgery to avoid threatening rupture of the hepatic lesion and confirm the definitive pathohistological diagnosis (2, 11). In our case, due to the pregnancy, preoperative chemotherapy was not chosen, and we planned ultrasonographic and MRI follow-ups, scheduling surgery after childbirth. Considering the risk of spreading the disease and tumor mass rupture during percutaneous biopsy, we relied on overall clinical and radiological features for tumor assessment.

Literature suggests that treatment for thymoma metastases in the liver typically involves surgical resection, followed by chemotherapy and occasionally radiotherapy, although evidence is lacking, especially concerning liver metastasis incidence (3).

In conclusion, our management of liver metastatic thymoma consisted of staged hepatectomy followed by systemic chemotherapy based on the lymphoma tumor board's recommendation. Further studies are needed to precisely understand neoplasm behavior like thymoma for timely detection and effective treatment.

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Licensing

Abbreviations

MRI – Magnetic Resonance Imaging
CT – Computed Tomography

Sažetak

METASTAZE TIMOMA U JETRI: PRIKAZ SLUČAJA BRZORASTUĆE ABDOMINALNE MASE KOD TRUDNICE

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Uvod: Timomi su najčešći, primarni tumori medijastinuma koji potiču iz epitelnih ćelija timusa, odnosno ćelija sa epitelnom diferencijacijom. Kada je reč o njihovom biološkom ponašanju, timomi se odlikuju relativno sporim rastom i sposobnošću da se obično direktno šire, sa nepoznatom incidencijom davanja udaljenih metastaza pogotovo u ekstratorakalnim organima. Udaljene metastaze, posebno u jetru, su izuzetno retke i postoji samo nekoliko slučajeva opisanih u literaturi.

Prikaz slučaja: Naša pacijentkinja, 39-godišnja žena u 31. gestacijskoj nedelji trudnoće, imala je bol i nelagodnost u trbuhu i upućena je na ultrazvučni pregled praćen hitnom MR abdomena zbog tumorske mase u jetri. Ubrzo nakon što je na svet carskim rezom donela jedno zdravo dete, primljena je u bolnicu gde je urađen CT abdomena. Snimci su pokazali nekoliko fokalnih promena u parenhima jetre, sa radiološkim karakteristikama koje bi najpre odgovarale fokalnoj nodularnoj hiperplaziji, manje verovatnim adenomima ili hemangiomima. Operisana je gde je urađena etapna hepatektomija, a rezultati patohistoloških analiza su pokazali da se radi o metastazama timoma tipa B u jetri.

Zaključak: Prema podacima dostupnim u literaturi, metastatski timomi se uglavnom otkrivaju i očekuju kod pacijenata koji su prethodno lečeni od primarnog oblika bolesti. Prema prethodnoj istoriji bolesti naše pacijentkinje, što je potvrđeno i postoperativnim skenerom grudnog koša, pacijentkinja ranije u životu nije imala timektomiju. S obzirom na kasnu trudnoću kao period kada su se javili simptomi, odlučili smo da se oslonimo na ukupne kliničke i radiološke karakteristike otkrivenog tumora. Naš tretman se sastojao od etapne hepatektomije nakon porođaja, nakon čega je usledila postoperativna hemoterapija. Neophodne su dalje i veće studije kako bi se precizno utvrdilo ponašanje neoplazmi kao što je timom kako bi se blagovremeno otkrile i efikasno lečile.

***Ključne reči**:* timom, metastaze, jetra, trudnoća, hirurgija.

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Case report

SMALL BOWEL CONTUSION AND PERFORATION DUE TO UNCOMMON BLUNT ABDOMINAL TRAUMA

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Abstract: **Introduction:** Small bowel injuries are rare, accounting for only 1% - 5% of injuries following blunt abdominal trauma, while small bowel perforation has been reported in 0.3% of patients. Delays in early diagnosis or misdiagnosis significantly contribute to the mortality and morbidity associated with small bowel injuries. Blunt abdominal trauma poses a diagnostic challenge, with focused assessment using sonography in trauma and computed tomography abdomen becoming invaluable methods for diagnosis, integrated into management guidelines.

Case Report: We present a case of jejunal perforation and contusion resulting from blunt abdominal injury due to a fall onto a fence. The initial chest X-ray did not reveal any traumatic injuries or subdiaphragmatic free gas. Computed tomography of the abdomen and small pelvis revealed free fluid in the peritoneal cavity and thickening of the jejunal wall, corroborated by abdominal ultrasound. Surgical intervention confirmed a diagnosis of small jejunal perforation.

Conclusion: Given the minimal and often clinically undetectable signs in patients with blunt abdominal trauma, timely and accurate imaging diagnostics and prompt surgical intervention significantly reduce the morbidity and mortality associated with these injuries.

Keywords*:* Blunt abdominal trauma, Jejunal perforation, Contusion, Computed tomography, Surgery.

INTRODUCTION

Trauma stands as the leading cause of mortality among individuals aged 1 to 44 years (1). In blunt abdominal trauma (BAT), small bowel and mesentery injury (SBMI) rank as the third most prevalent organ injury, following liver and spleen injuries. SBMI in blunt abdominal trauma constitutes a mere 1% - 5% of cases, with seatbelt injuries from motor vehicle accidents being the predominant mechanism in urbanized regions (2).

Blunt abdominal trauma often poses diagnostic challenges, complicating early recognition. Computed tomography (CT) serves as the gold standard for evaluating BAT, revealing various direct and indirect imaging signs indicative of bowel injuries documented in the literature. Signs such as wall discontinuity, enteric luminal contrast extravasation, extraluminal air, wall thickening, differential bowel wall enhancement, and the presence of free intraperitoneal fluid or mesenteric fat stranding are identified markers of traumatic bowel injuries.

Preoperative identification and localization of small bowel perforations typically present challenges, often remaining unclear before surgery. Thorough exploration of the entire small intestine by the surgeon is pivotal to detecting all potential injuries.

Here, we present a case involving a 22-year-old man who experienced jejunum perforation and contusion following a rare blunt abdominal injury, emphasizing diagnostic methods and operative treatment.

CASE REPORT

A 22-year-old man was admitted to the Emergency Surgery at the University Clinical Center of Serbia following blunt trauma to the abdomen from a fall onto a fence. Upon abdominal examination, the patient exhibited tenderness in the left upper quadrant during palpation. Laboratory results revealed an elevated white blood cell count of $19.1x10^9$ ($3.4\text{-}9.7x10^9$/L),

with other parameters within the normal range. A chest X-ray showed no evidence of traumatic injuries or subdiaphragmatic free gas (Figure 1). Focused assessment with sonography in trauma (FAST) indicated a 10 mm thickening of the jejunal wall in the left hemiabdomen, increased echogenicity around the mesentery, and a small amount of free fluid between

Figure 1. *Chest X-ray showing no signs of pneumoperitoneum*

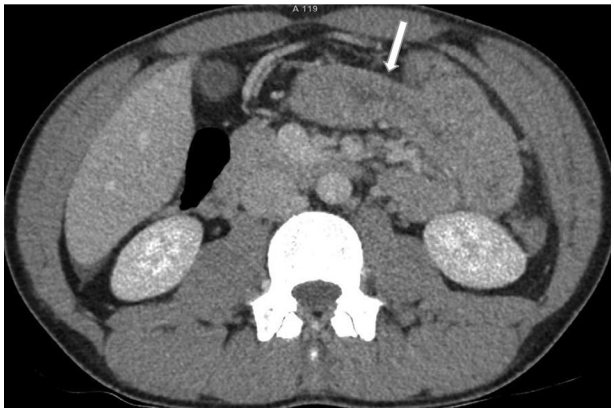

Figure 2. *Post-contrast phase in axial section - circumferentially thickening of jejunal wall (arrow)*

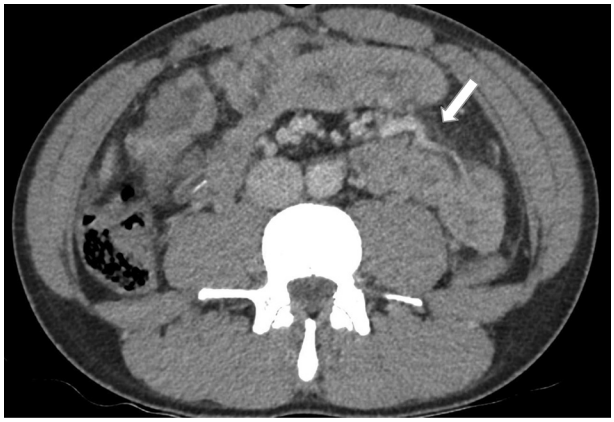

Figure 3. *Post-contrast phase in axial section – fat stranding in the mesentery (arrow)*

Figure 4. *Post-contrast phase in axial section – pelvic free fluid (arrow)*

loops, including the supravesical space. Subsequent abdominal and pelvic CT with intravenous contrast confirmed circumferential thickening and edema of the jejunal wall measuring 10 mm, alongside mesenteric "fat stranding" (Figures 2 and 3). The bowel wall displayed robust post-contrast opacification with serosal enhancement of the jejunum. The CT scan identified a substantial volume of pelvic free fluid and a small quantity between the jejunal loops and the subhepatic space (Figure 4). Other bowel loops appeared normal without visible signs of solid organ damage or extraluminal free air. The CT findings led to a diagnosis of jejunal contusion. An emergency laparotomy revealed an 8-9 mm diameter perforation in the jejunum, approximately 20 cm from the Treitz ligament. A moderate amount of serohemorrhagic intraperitoneal free fluid was drained, followed by suturing of the perforation site using a two-layer technique. The patient was discharged one week later after an uneventful postoperative recovery.

DISCUSSION

Small bowel perforation, as a part of BAT, is a rare condition reported in 0.3% of patients (3). The initial clinical examination might pose challenges and imprecisions; signs of bowel injury might manifest after several hours or even days. The nearly neutral pH of the small bowel content, along with reduced enzyme activity and low bacterial density, leads to the slow development of peritoneal inflammation. Moreover, undetected and delayed diagnosis of SBMI significantly correlates with increased mortality and morbidity (2).

The diagnostic methods for blunt abdominal trauma with suspected SBMI include diagnostic peritoneal lavage, FAST, and CT. FAST, being a non-invasive and rapid method to detect intraperitoneal fluid, serves as a widespread diagnostic modality for trauma patient evaluation. According to Kahn et al, the presence of intra-abdominal free fluid detected on FAST, without injury to a solid organ, indicates a high suspicion of

SBMI. However, the authors emphasize that the presence of free peritoneal fluid is not a specific finding indicative of bowel injury (4). CT has emerged as the standard imaging modality for hemodynamically stable and high-risk patients with BAT (5). In a study involving 11,924 blunt trauma patients, bowel wall thickening and mesenteric stranding were found to be the second most frequent sensitive signs for bowel injury, following free peritoneal fluid. The authors highlight pneumoperitoneum, bowel wall hematoma, and oral contrast extravasation as highly specific signs of bowel injury. However, though pneumoperitoneum is recognized as a direct sign of bowel injury, another study reported its lack of direct association with small bowel perforation in SBMI patients (6,7). Perforation might occur in cases where a small bowel perforation is contained, temporarily covered, or involves only the leakage of liquid content. The presence of an intramural hematoma with a significant mass effect on adjacent structures strongly suggests blunt trauma to the bowel wall. Notably, thickening of the small bowel might also occur in non-traumatic intramural hematoma due to edema.

In our case, CT didn't reveal pneumoperitoneum or intramural hematoma, known as highly specific signs of bowel injury. Conversely, in the absence of specific CT indications for traumatic bowel and mesentery injury, the presence of indirect signs, like mesenteric stranding with bowel wall thickening, raises significant concern for bowel injury (8). In the context of jejunal contusion and perforation following BAT, the circumferential thickening of the jejunal wall with fat stranding between loops and free intra-abdominal fluid are notable features in our case.

Depending on the technical equipment and the surgeon's experience, exploration of the abdomen can be performed laparoscopically or through an open approach. According to the guidelines issued by the American Association for the Surgery of Trauma (AAST), small bowel perforations are categorized as gradus II (involving less than 50% of the bowel circumference) and gradus III (over 50% of the bowel circumference) (9). Surgical management of bowel perforation can vary according to AAST recommendations, ranging from simple primary closure to delayed restoration of bowel continuity. Although a thorough examination of the injured part of the intestine should be conducted in detail (assessing the condition of the defect edges and possible presence of a hematoma in the mesentery), in most cases, grade II injuries can be managed with primary sutures, while more extensive defects (gradus III) are treated by resection and anastomosis. To perform a primary closure (suture or anastomosis), the bowel wall must be free from trauma, inflammation, or necrotic tissue. In cases where the bowel's condition or the patient's health is compromised, the risk of anastomosis or closure failure can be excessively high, making the exteriorization of the bowel defect a much safer primary measure. Patients with severe peritonitis, multi-organ failure, or poor mesenteric circulation should not be considered for primary anastomosis. The failure of an anastomosis could result in the patient's condition deteriorating, potentially leading to death. In such cases, some form of exteriorization, such as a double-lumen common stoma, allows postoperative monitoring of bowel vitality. The closure of the stoma, along with the re-establishment of bowel continuity, is a straight forward procedure that does not require additional laparotomy.

CONCLUSION

Recognition of highly sensitive and specific imaging signs is crucial in diagnosing bowel injuries following BAT. Early utilization of imaging diagnostics and prompt surgical intervention play pivotal roles in reducing the morbidity and mortality associated with these injuries, despite the often subtle clinical manifestations observed in BAT patients.

Abbreviations

SBMI — Injuries of the small bowel and mesentery

CT — Computed tomography

BAT — Blunt abdominal trauma

FAST — Focused assessment with sonography in trauma

AAST — American Association for the Surgery of Trauma

Patient Consent

We obtained verbal and signed consent from the patient to publish the case report. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments.

Author Contribution

All listed authors have made substantial contributions to all parts of the manuscript.

Conflict of Interest Statement

All authors disclose that they have no conflicts of interest related to this study.

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None

Sažetak

KONTUZIJA I PERFORACIJA TANKOG CREVA USLED RETKE TUPE TRAUME ABDOMENA

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Uvod: Povrede tankog creva su retke i čine samo 1%-5% povreda nakon tupe traume abdomena, dok je perforacija tankog creva zabeležena kod 0,3% pacijenata. Usled odložene pojave kliničkih znakova traumatske povrede creva, inicijalni klinički pregled može biti otežan i nespecifičan. Odlaganje rane dijagnoze ili netačna dijagnoza su dva glavna razloga mortaliteta i morbiditeta povezenih sa povredama tankog creva. Tupa trauma abdomena često predstavlja dijagnostički izazov. Ultrazvuk po FAST protokolu i kompjuterizovana tomografija zauzimaju značajno mesto u dijagnostici pacijenata sa tupom abdominalnom traumom.

Prikaz slučaja: Predstavljamo slučaj perforacije i kontuzije jejunuma nakon tupe traume abdomena, uzrokovane padom na ogradu. Prvobitni rendgenski snimak grudnog koša nije ukazivao na traumatsku povredu, niti na prisustvo pneumoperitoneuma. Urađena je komjuterizovana tomografija abdomena i karlice koja je pokazala prisustvo intraperitonealne slobodne tečnosti i zadebljanje zida jejunuma, što je viđeno i ultrazvučnim pregledom. Indikovana je operacija i dijagnoza perforacije jejunuma je potvrđena.

Zaključak: Zbog nespecifičnih i odloženih kliničkih znakova nakon tupe abdominalne povrede, pravovremena i pravilna imidžing dijagnostika kao i operativno lečenje zničajno smanjuju morbiditet i mortalitet ovih pacijenata.

***Ključne reči**:* Tupa trauma abdomena, Perforacija jejunum, Kontuzija, Kompjuterizovana tomografija, Hirurgija.

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Case report

SUBACUTE MASSIVE PULMONARY THROMBOEMBOLISM IN YOUNG PATIENTS: A COMPARATIVE PRESENTATION

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Abstract: **Introduction:** Subacute massive pulmonary embolism is a potentially fatal condition that can manifest in various clinical ways in a young patient, from mild and nonspecific to lethal. The incidence of pulmonary embolism in the younger population should not be overlooked, whether it involves individuals with certain risk factors, either genetic or acquired, or individuals with unidentified risk factors.

Case Presentation: We are presenting two young patients, aged 35 and 37, who had a protracted course of disease and clinical manifestations at least 15 days before admission. The first patient had nonspecific pains and sensations in the chest area and coughed up blood on two occasions. The day before admission, he had an intense one-hour swimming workout. The second patient had rapid fatigue and choking, which led to an echocardiogram of the heart and a treadmill test that was terminated at the second level due to poor condition, as stated by the patient himself. He came in due to intense pain in the epigastrium, preceded by a loss of consciousness. In both patients, a diagnosis of massive PTE was made: the first by Multi-Slice Computed Tomography of the pulmonary artery (MSCTPA) and the second by clinical autopsy. The first patient received thrombolytic therapy and was discharged with NOACs (Apixaban) after 10 days of hospitalization.

Conclusion: It is always necessary to keep in mind the possibility of PTE, even in younger patients and in cases with subtle clinical presentations, even without identified predisposing factors.

Keywords*:* pulmonary thromboembolism, subacute, massive, MSCTPA, risk factor, genetic, acquired, unidentified.

INTRODUCTION

Pulmonary Thromboembolism (PTE) is the foremost avoidable cause of mortality in patients admitted to the hospital (1). Furthermore, it ranks as the third most common cause of cardiovascular-related deaths, following myocardial infarction and cerebrovascular accidents (strokes). Subacute massive PTE is defined as the onset of symptoms for 2-12 weeks and a pulmonary angiogram showing massive pulmonary embolism (≥ 50% obstruction in the main pulmonary arteries) (2). Idiopathic Venous Thromboembolism (VTE) is defined as "any VTE" in the absence of an identified predisposing factor (3).

The current literature review suggests that the frequency of PE in the younger population should not be overlooked, whether they are individuals with certain risk factors, either genetic or acquired, or individuals with unprovoked factors. A retrospective observational study following pulmonary embolism (PE) in the 18-45 age group across five years in a district general hospital revealed that 17.1% of patients had unprovoked disease (4). Treating unprovoked PE requires consideration for further investigation into potential disease etiology. The current review of the literature suggests that the incidence of PE in the younger population should not be overlooked, whether it involves individuals with certain risk factors, genetic or acquired, or individuals with unprovoked factors. In a 2007 study conducted by Sakuma and colleagues, an analysis of autopsy records revealed that Pulmonary Embolism (PE) was responsible for 2.3% of all fatalities within 20 to 39 years of age (5). Only 20% of PE detected at autopsies was diagnosed during life. The death rate for diagnosed and managed pulmonary embolism fluctuates between 3 and 8%. However, if left untreated, this rate can surge to roughly 30% (6). The wide range of clinical symptoms associated with this condition complicates its diagnosis. Additionally, treatment approaches can differ significantly, and the unpredictability of the outcomes leads to high rates of morbidity and mortality.

This article presents two young patients with distinct clinical manifestations of subacute massive PTE.

CASE REPORT No 1

A 35-year-old patient presented to the Emergency Center of the Clinical Center of Serbia (UCCS) due to nonspecific left-sided chest pain persisting for two weeks and coughing up blood-streaked sputum on two occasions. A chest X-ray conducted at the local Health Center exhibited a slight pathological finding (Figure 1), accompanied by an elevated CRP level of 41.8mg/l (cut-off 5), prompting referral to the UCCS Emergency Center.

The patient was hemodynamically and respiratory stable (blood pressure (BP) 130/70 mmHg, SpO_2 98% on room air, heart rate 70/min, body mass index (BMI) 27.7 kg/m^2), with a normal ECG (Figure 2A), normal heart sounds on auscultation, and reduced breath sounds over the left basis of the lung. A CT pulmonary angiogram was immediately performed, which revealed a massive thrombus at the bifurcation of the pulmonary artery with propagation into both main, lobar, and segmental branches, along with a left-sided pleural effusion (9 mm thick), a ratio of Ao/pulmonary artery of 0.8 with slight reflux of contrast into the inferior vena cava (IVC) - signs of right heart strain (Figure 3).

The patient was admitted to the coronary intensive care unit, where an echocardiogram indicated severe pulmonary hypertension (with a floating thrombus at the pulmonary artery bifurcation and its right branch, RV diameter: 3.0 cm, AccT: 59 msec). Alteplaza was administered intravenously at 100mg, 50ml/h for 2h, as per protocol.

During hospitalization, laboratory analyses showed elevated D-dimer levels (11.2 mg/l, cut off 0,5) and slightly elevated inflammation parameters. A Doppler ultrasound of the lower extremities was also performed, which did not show thrombotic masses in the lower extremities. After ten days, the patient was discharged with advice for continued home treatment with dual anticoagulant therapy (Apixaban). However, he did not undergo the recommended hematological examination.

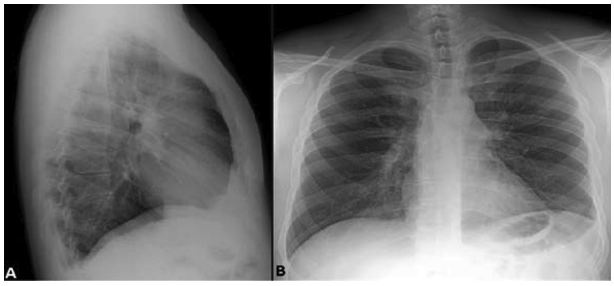

Figure 1. *Prominent arch of the pulmonary artery in the cardiac bay. 2. Amputated lower pole of the left hilus shadow 3. Discreetly elevated left hemidiaphragm 4. Flattened left KF sinus and posterior left Costo-diaphragmatic angle*

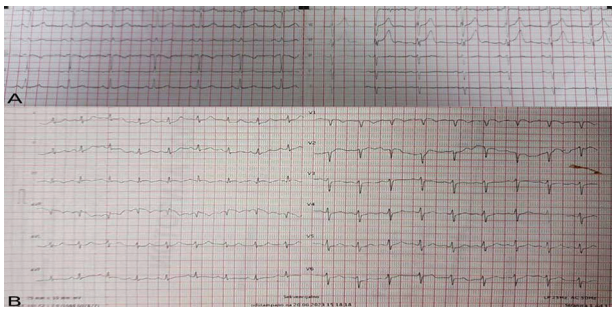

Figure 2. *A) ECG, case 1. sinus rhythm, heart rate 75/min, early repolarization in V1-3, B) ECG, case 2. sinus rhythm, heart rate 108/min, ST depressions up to 1mm in D1, D3, aVL, and precordial leads, aVR minimal ST elevation*

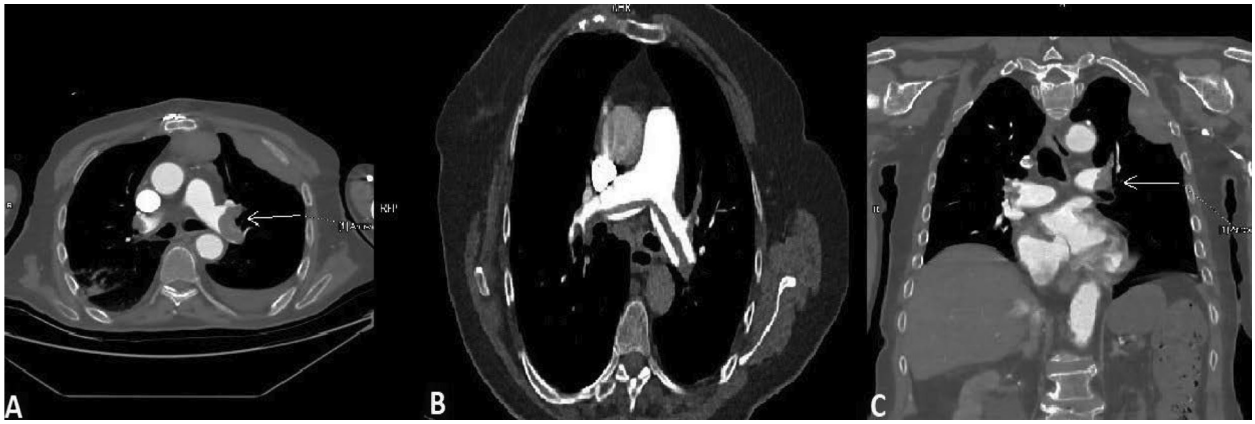

Figure 3*. Massive thrombus at the bifurcation of the pulmonary artery with propagation into both main A) Axial section, PTE in the main branches, B) Axial section, "saddle thrombus", C) Coronal section, PTE in the main branches*

Figure 4. *Floating thrombus is at the bifurcation of the pulmonary artery and its right branch*

CASE REPORT No 2

A 37-year-old patient was brought to the Emergency Center of the Clinical Center of Serbia (UCCS) due to a fall, following a loss of consciousness preceded by severe epigastric pain. He reported that he had been examined by a cardiologist due to chest pain and rapid fatigue that had lasted for 15 days, an echocardiographic examination had been performed which was normal, and an exercise stress test was stopped at the second stage (due to poor physical condition, as he was been told). Additionally, the patient had a known medical history of hypertension and insulin resistance.

Upon admission to the Emergency Center, the patient was conscious, pale, hypotensive (BP 80/55 mmHg), tachycardic (108/min), normal-saturated on room air (SpO_2 95%), with a of BMI 30.9 kg/m^2. Physical examination revealed a laceration-contusion wound at the root of the nose and epigastric tenderness on light touch. Auscultation showed normal heart and lung sounds. The ECG indicated sinus rhythm, a heart rate of 108/min, ST depressions of up to 1mm in D3, aVL, and precordial leads, and minimal ST elevation in aVR (Figure 2B).

Immediately upon admission, an abdominal ultrasound was performed, which did not indicate acute pathological events. Due to severe epigastric pain, a CT scan of the abdomen and pelvis was indicated, during which the patient experienced a disturbance of consciousness and cardiac arrest. Despite resuscitation efforts, cardiac activity was not re-established, resulting in a lethal outcome. A clinical autopsy was requested, which confirmed the presence of massive pulmonary thromboembolism. Subsequent laboratory analyses revealed a D-dimer level of 25.56 mg/l (cut-off 0.5), with other parameters within the reference range.

Verbal and signed consent was obtained for the publication of this case report. All procedures conducted adhered to the principles outlined in the 1964 Helsinki Declaration and its subsequent amendments.

DISCUSSION

We have presented two young men who had subacute massive PTE and who reported to the Emergency Center of the UCCS about 15 days after the onset of their symptoms. The contributing factors for subacute pulmonary embolism are often unidentified (7) and could lead to repeated embolisms. There's a noticeable lack of studies focusing on risk factors in younger demographics (8, 9). Both patients had a nonspecific, protracted course of the disease, which had a similar duration and in which symptoms sometimes lessened and sometimes intensified. Those who undergo a subacute progression of the illness face a higher death rate and a greater occurrence of thromboembolic hypertension compared to patients with an acute onset of the disease (2).

The first patient had nonspecific pain and coughed up blood on two occasions, so the diagnostic algorithm started from laboratory analyses, with slightly elevated CRP and X-ray of the heart and lungs, which showed a discrete pathological finding. For an experienced radiologist, the alarm was pleural effusion and mild elevation of the hemidiaphragm in an otherwise healthy individual. Since there were no signs of heart failure and signs of malignancy, the next serious differential diagnosis was PTE.

The second patient had difficulty breathing and fatigue that lasted at least 15 days, which led to a transthoracic echocardiogram and a physical stress test, which was interrupted at the second stage due to poor condition, as it was interpreted at the time. Troponin, a biomarker of cardiac necrosis, was also performed, which was within the reference range. The protracted and insidious symptoms led to a delay in diagnosis and treatment, which was fatal in the case of this young man.

A retrospective observational analysis of a younger demographic (age $\leq$ 45 years) revealed that the predominant clinical manifestations were dyspnea, thoracic discomfort, and cough (10). In a review of 61 instances of lethal pulmonary thromboembolism, the primary clinical presentations observed were dyspnea, syncope, lower extremity discomfort, and chest pain (11).

The term "massive PTE," refers not to the embolism's size but to its hemodynamic consequences, with individuals experiencing hemodynamically unstable pulmonary embolism being at an elevated risk of succumbing to obstructive shock, as a result of acute pressure overload inducing severe right ventricular in-

sufficiency (12). Right ventricular dysfunction, which can be evaluated via echocardiography or MSCT PA, has been linked to elevated mortality rates. However, it is posited that echocardiography provides a more dependable diagnostic approach compared to MSCT.

A meta-analysis of seven studies involving 3395 normotensive and hypotensive patients with PE reported that right ventricular dysfunction is associated with a doubling of hospital mortality from PE (13). Nonetheless, a subset analysis of normotensive patients indicated a weak correlation between right ventricular dysfunction, as detected via echocardiography or MSCT, and mortality. This suggests that it's the symptomatic manifestation of right ventricular dysfunction that serves as a predictor for mortality.

In our normotensive patient, asymptomatic right ventricular dysfunction was observed, and the prognosis appeared favorable. Elevated BNP, NT-proBNP, and troponin in hemodynamically stable patients do not reliably predict fatal outcomes. However, when these markers fall within normal or low ranges, they consistently indicate a benign clinical trajectory (14).

Upon arrival at the emergency department, the first patient was in good general condition. Over 95% of patients with acute PE are (or appear to be) hemodynamically stable at the time of presentation, so they are not considered to be at high risk (15). The second patient suffered severe epigastric pain, after a previous loss of consciousness. In literature, abdominal pain is also described as a rare and atypical manifestation of PE (16), the mechanism of which is still not sufficiently researched. It is believed that it most likely occurs due to liver congestion and consequent distension of Glisson's capsule, as well as due to pleuritis resulting from lung infarction at the base of the lung.

The first patient underwent MSCT PA due to high clinical suspicion, revealing a saddle thrombus. Unfortunately, the second patient died during the diagnostic process before a conclusive CT diagnosis was reached. MSCTPA remains the preferred diagnostic method for suspected PTE, boasting a sensitivity of 83% and specificity of 96% according to PIOPED (Prospective Investigation on Pulmonary Embolism Diagnosis) (17).

The Pulmonary Embolism Rule-out Criteria (PERC) is particularly valuable in risk stratification, especially in younger patients, aiming to prevent unnecessary MSCT PA imaging. PERC allows healthcare professionals to identify patients at low risk of PTE, eliminating the need for further testing, including D-dimer assays. Criteria include age under 50 years, heart rate below 100 beats per minute, oxygen saturation (SpO_2) equal to or above 95%, no hemoptysis, no estrogen use, no history of surgery or trauma requiring hospitalization in the last four weeks, absence of prior venous thromboembolism (VTE), and no unilateral leg swelling. The effectiveness of this rule was substantiated in a prospective study conducted from 2003 to 2006, where the false-negative rate for PTE was found to be 1.2% (18).

In cases of subacute, massive PE where there is no hemodynamic instability, the decision to initiate fibrinolysis primarily relies on MSCT PA findings. There is a tendency for subacute PE to show a less robust response to thrombolytic therapy compared to acute PE, likely because an older thrombus has less plasminogen compared to a more recent one (7).

Thrombolytic therapy has demonstrated a quicker alleviation of pulmonary obstruction, with a significant associated reduction in the risk of circulatory collapse. However, this comes with an increased risk of severe extracranial and intracranial hemorrhage (19). The International Cooperative Pulmonary Embolism Registry has reported a notably high incidence of intracranial bleeding - 3% among patients with PE who were treated with thrombolytic therapy (20). Early thrombus withdrawal early recovery of right ventricular function and reduction of PAH were seen in our patient who received Alteplase. In a randomized trial, Goldhaber (21) found an improvement in right ventricular function after 24 hours in 16/18 patients with thrombolysis compared to 8/18 treated with heparin.

Both of our patients had an elevated BMI, in the category of overweight to obesity. It remains an open question whether studying potentially causal mechanisms (chronic inflammation, adipokines, decreased fibrinolytic activity, procoagulant microparticles, polycythemia) (22) can reduce the percentage of idiopathic VTE in young patients.

CONCLUSION

Subacute massive PTE requires a good understanding of a wide range of clinical presentations, from very mild and inconspicuous to typical and pronounced. It requires connecting clinical manifestations over a prolonged period into one unit and category. Finally, it requires efficient and appropriate treatment and the search for unknown predisposing factors for young people, as a requirement for future multicenter investigations.

Abbreviation

BMI – body mass index
BP – blood pressure
IVC – inferior vena cava
MSCT – Multi-slice Computed Tomography
MSCT PA – Multi-Slice Computed Tomography of the Pulmonary Artery

PE – pulmonary embolism
PTE – pulmonary thromboembolism
RV – right ventriculus
UCCS – University Clinical Centre of Serbia
VTE – venous thromboembolism

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Licensing

Sažetak

SUBAKUTNA MASIVNA PLUĆNA TROMBOEMBOLIJA (PTE) - KOMPARATIVNI PRIKAZ

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Uvod: Subakutna masivna plućna tromboembolija je životno ugrožavajuće stanje koje može imati kod mladog pacijenta različite načine kliničkog ispoljavanja, od blagog i nespecifičnog do letalnog. Učestalost PE u mlađoj populaciji ne treba zanemariti, bilo da su u pitanju pojedinci sa određenim faktorima rizika, genetskim ili stečenim, bilo da su u pitanju pojedinci sa neidentifikovanim faktorima rizika.

Prikaz slučaja: Prikazujemo 2 mlada pacijenta, starosti 35 i 37 godina, koji su imali protrahovan tok bolesti i klinička ispoljavanja najmanje 15 dana pre prijema. Prvi pacijent je imao nespecifične bolove i senzacije u predelu grudnog koša i u dva navrata iskašljao sukrvicu. Dan pred prijem imao je intenzivan jednočasovni plivački trening. Drugi pacijent je imao brzo zamaranje i gušenje, zbog čega je rađena ehokardiografija srca i test fizičkog opterećenja koji je prekinut na drugom stepenu (zbog loše kondicije, kako mu je rečeno). Došao zbog intenzivnog bola u epigastrijumu, sa posledičnim gubitkom svesti. Kod oba pacijenta dijagnostikovana je masivna plućna tromboembolija, kod prvog na multislajsnom skeneru plućne arterije, a kod drugog na kliničkoj obdukciji. Prvi pacijent je dobio trombolitičku terapiju i otpušten iz bolnice posle 10 dana.

Zaključak: Potrebno je uvek imati na umu plućnu tromboemboliju, i kod mlađih pacijenata, i kod neupadljive kliničke slike, i bez identifikovanih predisponirajućih faktora.

Ključne reči: plućna tromboembolija, subakutna, masivna, multislajsni skener plućne arterije, faktor rizika, genetski, stečeni, neidentifikovani.

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Review article

VITAMIN D LEVELS AND VDR rs2228570 GENETIC VARIANT IN AUTOIMMUNE THYROIDITIS

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Abstract: Autoimmune Thyroiditis (AIT) is a prevalent autoimmune disorder characterized by an immune response targeting the thyroid gland. Genetic factors play a significant role in AIT susceptibility, with immune-related genes, especially the vitamin D receptor (VDR) gene, potentially influencing AIT development. This comprehensive review delves into the intricate association between VDR gene polymorphisms, particularly rs2228570 (FokI), and AIT susceptibility, exploring various populations. Research has unveiled contrasting outcomes regarding the link between the VDR rs2228570 polymorphism and AIT risk across diverse ethnic groups. Certain populations have exhibited a noteworthy correlation, suggesting that population-specific genetic factors contribute to AIT risk. A recurring observation of vitamin D deficiency in AIT patients has correlated with elevated anti-thyroid antibodies, abnormal thyroid function, and thyroid volume. The results emphasize the possible role of vitamin D in the development of AIT, suggesting the importance of vitamin D supplementation to address deficiencies associated with AIT. In addition to VDR rs2228570, other genetic variants have also shown associations with AIT susceptibility, displaying varying results across different populations. Ethnicity emerges as a pivotal factor influencing these associations, underscoring the need to consider genetic variations in diverse populations. We emphasize the intricate interplay between VDR gene polymorphisms, vitamin D, and AIT susceptibility. Extensive research is essential to unveil the clinical significance of these genetic variations, offering prospects for enhanced diagnostic and therapeutic strategies for individuals with AIT.

Keywords*:* VDR Gene, SNP, Vitamin D, Autoimmune Thyroiditis.

INTRODUCTION

Autoimmune thyroiditis (AIT) is a widespread pathological condition characterized by an autoimmune response targeting the thyroid gland (1,2). Genetics is a key factor contributing to the development and progression of AIT (3). Research suggests that various immune-related genes play a role in the genetic predisposition to Autoimmune Thyroiditis (AIT) (4). The vital involvement of the vitamin D receptor (VDR) and its system is integral to the inflammatory response mechanism that leads to autoimmunity. Among autoimmune thyroid diseases (AITDs), Hashimoto's Thyroiditis (HT), or Autoimmune Thyroiditis (AIT), stands out as the most widespread manifestation. The origins of AIT are multifaceted and not entirely understood. However, it is widely believed that there is an interplay between environmental factors and genetic predisposition in its development (5).

Environmental factors, including the use of certain medications, iodine intake, exposure (6) to radiation (7), viral infections (8), and hormonal influences (9), can directly impact the function of thyrocytes. These factors may have detrimental effects on the immune system and can disrupt its normal functioning, leading to the development of AIT. Overall, the pathogenesis of AIT involves a complex interplay between genetic factors, particularly immune-related genes, and environmental influences. Additional investigation is required to clarify the complex mechanisms underlying the development and progression of AIT, which could potentially lead to improved diagnostic and therapeutic approaches for individuals affected by this autoimmune thyroid disorder. Genetic factors play a significant role, accounting for approximately 70-80% of the disease development in autoimmune disorders. Like many other autoimmune diseases, certain conditions, such as autoimmune thyroiditis (AIT), affect females more frequently. Vitamin D is now recognized for its pleiotropic effects, meaning it has multiple functions and impacts various aspects of health. The literature confirms the potential link between vitamin D and the

incidence of thyroid diseases, specifically autoimmune thyroid diseases (AITD) (10).

Moreover, the correlation between vitamin D receptor (VDR) polymorphism and various autoimmune disorders has been extensively studied. VDR polymorphisms have also been implicated in autoimmune thyroiditis. However, the impact of VDR single nucleotide polymorphisms (SNPs) on susceptibility to autoimmunity can vary among different populations and ethnicities. VDR gene SNPs have a significant contribution to numerous diseases (11). It is important to note that further research is needed to fully understand the specific mechanisms by which VDR SNPs influence autoimmunity and their potential implications for individuals with autoimmune thyroiditis. The interplay between genetic factors, vitamin D, and their association with autoimmune disorders is a complex and evolving field of study. The Vitamin D receptor (VDR) is a receptor located within the cell nucleus. The VDR gene is on chromosome 12q13.1 and comprises 11 exons (12). Researchers have focused their investigations on genetic variations in the regulatory regions of the VDR gene, collectively known as VDR polymorphisms. These polymorphisms involve changes in a single nucleotide and have been extensively studied in relation to various diseases, including AITDs. Approximately sixty VDR SNPs have been identified thus far. Some notable SNPs associated with an increased risk of AITD include FokI rs2228570, ApaI rs7975232, TaqI rs731236, and BsmI rs1544410. In addition, these genetic variants have been linked to a higher susceptibility to developing AITD. In this review, we summarize the association between Vitamin D and VDR gene genotypes.

VITAMIN D LEVELS IN AUTOIMMUNE THYROIDITIS

Vitamin D contributes significantly to numerous diseases (13, 14). Vitamin D, through its active form 1,25(OH)2D, exerts regulatory influence over a wide range of biological functions, extending beyond maintaining bone mineral balance. These roles include overseeing hormone secretion, adjusting the immune response, and coordinating cellular proliferation and differentiation. Recently, there has been increasing recognition of the diverse functions of vitamin D and its active metabolites across various bodily tissues. This finding has led to the recognition that most tissues throughout the body possess receptors known as vitamin D receptors (VDRs), referring to the active form of vitamin D as 1,25 dihydroxy vitamin D [1,25(OH)2D] or calcitriol. These VDR-containing tissues are considered potential target areas, highlighting the multifaceted impact of vitamin D on the body's overall function (15).

Particularly, vitamin D suppresses proliferation and immunoglobulin production while inhibiting the differentiation of B cell precursors into plasma cells. This ability of 1,25(OH)2D to dampen the adaptive immune response offers advantages in situations where the immune system mistakenly targets the body's tissues, as seen in autoimmune disorders (16).

An analysis of a study conducted in the Hungarian population revealed markedly higher vitamin D deficiency among individuals diagnosed with autoimmune thyroid diseases (AITDs) compared to healthy individuals. Specifically, deficiency was found in 72% of AITD patients, while only 30.6% of healthy individuals exhibited the same condition ($P < 0.001$). Within the AITD group, patients with Hashimoto's thyroiditis displayed a higher prevalence of vitamin D deficiency than those with non-AITDs. Among Hashimoto's thyroiditis patients, 79% had a deficiency, whereas only 52% of non-AITD patients had the same deficiency ($P<0.05$). This analysis also revealed a correlation between vitamin D deficiency and the presence of antithyroid antibodies, indicating an association between these factors ($P = 0.01$). Additionally, abnormal thyroid function tests were linked to vitamin D deficiency, although the correlation was slightly weaker ($P = 0.059$). The analysis provided evidence of significantly low levels of vitamin D among patients with AITDs, particularly those with antithyroid antibodies and abnormal thyroid function tests. Recent research suggests vitamin D's involvement in AITD development and indicates potential benefits of vitamin D supplementation for managing these conditions (17).

In an investigation of the relationship between 25OHD levels and Hashimoto's thyroiditis (HT) in three groups - HT patients on L-thyroxine (LT), newly diagnosed HT patients, and healthy volunteers - the results demonstrated that HT patients on levothyroxine (LT) had significantly diminished levels of 25-hydroxyvitamin D (25OHD) compared to both recently diagnosed HT patients and healthy controls. Higher 25OHD levels were associated with larger thyroid volume and lower levels of anti-TPO and anti-TG antibodies. Severe 25OHD deficiency was observed in a significant proportion of HT patients as well as in a smaller percentage of the control group. Furthermore, the study identified gender differences, with female HT patients having the lowest 25OHD levels and male controls having the highest levels. The findings demonstrate that individuals with HT exhibit a higher occurrence and severity of vitamin D insufficiency than healthy controls. Additionally, the extent of 25OHD deficiency is associated with the duration

of Hashimoto's Thyroiditis (HT), thyroid volume, and antibody levels. These findings imply a possible involvement of 25OHD in the onset of HT and its progression towards hypothyroidism (18).

The level of 25(OH)D3 independently influences the presence of TPOAb in individuals with AITDs. A study in the Korean population revealed that patients with increased anti-thyroid antibodies had lower levels of serum 25(OH)D3 compared to those without elevated antibodies ($p < 0.001$). Interestingly, there was a negativecorrelation between 25(OH)D3 and anti-thyroid antibody (TPOAb) levels in the group with autoimmune thyroid diseases (AITDs) ($r = -0.252$, $p < 0.001$), but no such correlation was observed in the group without AITDs ($r = 0.117$, $p = 0.127$), after accounting for age, sex, and body mass index. Furthermore, the concentration of 25(OH)D3 was considered an independent causative factor linked to the presence of TPOAb in the AITDs group, even after considering other factors that could impact the presence of TPOAb.

In conclusion, this suggests that vitamin D deficiency is more closely associated with the level of anti-thyroid antibodies rather than the thyroid function itself. The study proposes vitamin D as an immunomodulatory agent in autoimmune thyroiditis, and further research is required to understand the mechanisms and establish clarity. Notably, a significant association between anti-thyroid antibody levels and 25(OH)D3 was observed only in the group with AITDs. This finding may be attributed to the Korean population's generally low vitamin D levels. Interestingly, the correlation between 25(OH)D3 levels and anti-thyroid antibodies is also observed within the range of vitamin D deficiency (19).

VITAMIN D LEVELS AND FOKI (rs2228570) SNP

Studies suggest that genes' SNPs, including the VDR gene SNP, are associated with numerous conditions (20-23). Research has revealed a correlation between serum vitamin D levels and the manifestation of AITDs. Studies have shown that individuals with lower serum vitamin D levels are more likely to exhibit symptoms of AITDs (24). As an immunomodulator, vitamin D plays a crucial role in initiating and progressing AITD. Patients with AITD often exhibit deficiencies in vitamin D levels. Additionally, a correlation exists between vitamin D deficiency and elevated levels of antithyroid antibodies and increased thyroid volume, influencing the duration and severity of HT, a common form of AITD (25).

The immunomodulatory properties of vitamin D and its impact on various disease manifestations, including AITD, underscore the need for further research. Understanding precisely how vitamin D deficiency influences AITD development and progression can aid in developing targeted interventions and personalized treatment strategies for individuals affected by these autoimmune thyroid disorders.

A study conducted in western Ukraine, including 153 patients with various thyroid disorders, revealed that patients diagnosed with hypothyroidism and possessing the AA genotype had notably lower levels of Vitamin D, decreased by 18.8%, irrespective of the underlying cause of their condition, whether postoperative or autoimmune. This finding suggests that low levels of Vitamin D contribute to the exacerbation of thyroid insufficiency in these individuals. Additionally, the study demonstrated that different thyroid pathologies exhibited variations in Vitamin D levels.

Comparing patient groups to a control group, individuals with postoperative hypothyroidism displayed significantly decreased Vitamin D levels, approximately 1.89 times lower. Similarly, patients with hypothyroidism induced by Hashimoto thyroiditis showed a significant reduction in Vitamin D levels, approximately 2.05 times lower than the control group (26).

These findings underscore the significance of Vitamin D in thyroid health and suggest that insufficient levels of this vitamin may contribute to the onset and development of autoimmune thyroid disorders, especially Hashimoto's thyroiditis. The study highlights differences in Vitamin D levels among various thyroid pathologies, indicating the need for tailored approaches to managing and treating these conditions.

In the Serbian population, a study involving 44 female patients diagnosed with Hashimoto's thyroiditis and exhibiting reduced or deficient Vitamin D levels showed a significant difference in the VDR-FokI polymorphisms compared to control subjects (p-value < 0.05). This finding suggests a notable correlation between the VDR-FokI polymorphisms and the development of Hashimoto thyroiditis. Moreover, individuals with the VDR-FokI polymorphism were at a higher risk of developing the disease, with an odds ratio of 4.472 (27).

Similarly, in the Asian population, particularly among the Japanese, investigating the CC genotype and C allele frequencies for the VDR rs2228570 polymorphism revealed interesting results. The researchers found a higher prevalence of these polymorphisms in Hashimoto thyroiditis patients with low serum Vitamin D levels compared to the healthy group (p-values = 0.0174 and 0.0458, respectively). The CC genotype was found to contribute to autoimmune thyroid destruction directly, while the C allele was associated with increased interleukin 12 (IL-12) production, leading to cytotoxic T cell and Th1 cell-mediated thyroid destruction (28).

This information sheds light on the underlying mechanisms and pathogenesis of the disease, suggesting that immune regulation mediated by VDR is suppressed in patients with Hashimoto thyroiditis.

Interestingly, a similar distribution of the VDR-FokI genotype was noticed in the Chinese and Japanese populations. Lin et al. illustrated that 36.7% of HT patients in the Chinese population had CC genotypes compared to only 23.3% in the control group. Furthermore, they also highlighted a notable disparity in the distribution of VDR SNP genotypes (p-value: 0.0458) (29).

In summary, these studies conducted on the Serbian, Japanese, and Chinese populations provide valuable insights into the role of VDR-FokI polymorphisms and VDR rs2228570 polymorphisms in the development and pathogenesis of Hashimoto thyroiditis. They establish a significant association between these genetic variations and the disease, highlighting the importance of immune regulation mediated by VDR in the occurrence and progression of Hashimoto thyroiditis.

Additionally, other SNPs in the VDR gene, including rs1544410 (BsmI), rs7975232 (ApaI), and rs731236 (TaqI), have shown associations with AITD. In particular, a study in the Southwest Chinese Han population indicated that the AA genotype and A allele of VDR/ApaI significantly correlate with an increased risk of developing Graves' disease (GD). However, no significant associations were found between GD and other polymorphisms, including FokI, TaqI, and BsmI. These findings suggest that VDR mRNA expression and levels of secreted cytokines may play a role in GD development (24).

A subsequent meta-analysis exploring the relationship between ethnicity and VDR polymorphisms revealed that the rs1544410 polymorphism is linked to an increased risk of AITD in Asian populations, while African and European populations demonstrated a decreased risk. Moreover, the rs731236 polymorphism was associated with an increased risk of AITD, encompassing Hashimoto's thyroiditis and Graves, in both Asian and African populations, while no significant relationship was detected in European populations. These findings emphasize the influence of VDR polymorphisms on AITD risk, varying based on ethnicity, highlighting the importance of considering genetic variations across different populations (30-35).

In conclusion, the altered Vitamin D levels and VDR SNP rs2228570 (FokI) may be considered potential risk factors for AITD susceptibility, though their association varies among different populations. The precise pathogenesis explaining this association remains unclear, emphasizing the need for further studies to determine the clinical significance of these genetic variations across diverse populations.

Abbreviation

AIT — Autoimmune thyroiditis;
VDR — Vitamin D receptor;
AITDs — Autoimmune thyroid diseases;
HT — Hashimoto Thyroiditis;
SNPs — Single Nucleotide Polymorphisms;
1,25(OH)2D — 1,25 dihydroxy Vitamin D;
LT — L-thyroxine;
25OHD — 25-hydroxyvitamin D;
Anti-TPO — Anti-thyroid peroxidase;
Anti-TG — Antithyroglobulin antibodies;
IL-12 — Interleukin 12;
GD — Graves disease;
PCR — polymerase chain reaction;
mRNA — messenger ribonucleic acid.

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Sažetak

NIVOI VITAMINA D I GENETSKI VARIANT VDR rs2228570 U AUTOIMUNOM TIREODITISU

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Autoimuni tireoiditis (AIT) je rasprostranjeno autoimuno oboljenje koje karakteriše imunološki odgovor usmeren protiv tireoidne žlezde. Genetski faktori imaju značajnu ulogu u podložnosti za AIT, pri čemu geni povezani s imunološkim sistemom, posebno gen za receptor vitamina D (VDR), potencijalno utiču na razvoj

AIT-a. Ova sveobuhvatna analiza istražuje kompleksnu povezanost između polimorfizama gena VDR, posebno rs2228570 (FokI), i podložnosti za AIT, istražujući različite populacije. Istraživanja su otkrila kontrastne rezultate u vezi sa povezanošću polimorfizma VDR rs2228570 i rizikom od AIT-a u različitim etničkim grupama. Određene populacije su pokazale značajnu korelaciju, sugerišući da specifični genetski faktori unutar populacija doprinose riziku od AIT-a. Ponavljano zapažanje nedostatka vitamina D kod pacijenata s AIT-om povezano je s povišenim antitireoidnim antitelima, poremećajem funkcije tireoidne žlezde i zapreminom žlezde. Rezultati naglašavaju moguću ulogu vitamina D u razvoju AIT-a, sugerišući važnost suplementacije vitamina D radi rešavanja nedostataka povezanih s AIT-om. Osim VDR rs2228570, i druge genetske varijante su pokazale povezanost s predispozicijom za AIT, prikazujući varirajuće rezultate u različitim populacijama. Etnicitet se ističe kao ključni faktor koji utiče na ove veze, ističući potrebu za razmatranjem genetskih varijacija u različitim populacijama. Naglašavamo kompleksnu međuigru između polimorfizama gena VDR, vitamina D i podložnosti za AIT. Obimna istraživanja su neophodna kako bi se otkrila klinička značajnost ovih genetskih varijacija, pružajući mogućnosti za unapređene dijagnostičke i terapijske strategije za osobe s AIT-om.

Ključne reči: Gen VDR, SNP, Vitamin D, Autoimuni Tireoiditis.

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UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

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Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

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Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada.

U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

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1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

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61

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